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Magnus Bolmsjö



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THE PHYSICAL AND PHYSIOLOGICAL ASPECTS
OF FEVER REPORTED IN EUROPEAN WARREN
APPLICATIONS

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Title and subtitle THE PHYSICAL AND PHYSIOLOGICAL ASPECTS OF XENON ISOTOPES IN NUCLEAR MEDICAL APPLICATIONS.			
Abstract A method for trapping radioactive xenon waste from nuclear medical departments has been investigated. Adsorption of xenon on activated charcoal was found to be an efficient trapping method. A large gain in capacity was found when the trap was refrigerated, and permitted a large number of patient investigations before break-through of xenon occurred. By heating charcoal traps to 250-350°C, adsorbed xenon gas is freed and is thus made available for re-use. A technique for room-air monitoring of xenon-leakage from patient investigations is described, where the room-air is continuously pumped through a small charcoal filter, mounted close to a detector. The low gammaenergy of Xe-133, 81 keV, introduces problems for <u>in vivo</u> measurements due to the small differences in the energies of the primary and Compton-scattered photons. Influence of scatter and of hemispheric cross-talk was studied for cerebral blood-flow measurements. It was shown that substantial artefacts are introduced in the calculation of regional gray matter flow. The applicability of the xenon-washout technique for liver blood-flow measurements in rat was investigated.			
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Signature Magnus Bolmsjö

Date 1981-10-14

To Ingrid, Clara and Erik

This thesis is based on the following papers, which in the text will be referred to by their Roman numerals.

- I Bolmsjö M. and Persson B.R.R.
Factors affecting the trapping performance of xenon holdup-filters in nuclear medicine applications.
Accepted for publication in Medical Physics.
- II Bolmsjö M. and Persson B.R.R.
Trapping and re-use system for radioactive xenon in nuclear medicine.
Phys. Med. Biol. 23:77-89, 1978.
- III Bolmsjö M. and Persson B.R.R.
A new instrument for survey monitoring of airborne Xe-133.
Submitted for publication 1981.
- IV Bolmsjö M.
Hemisphere cross-talk and signal overlapping in bilateral rCBF-measurements using Xe-133.
To be published.
- V Bolmsjö M., Hafström LO, Hugander A. and Persson B.R.R.
Measurement of blood flow in rat liver with Xe-133.
Submitted for publication 1981.

Preliminary reports from papers II, IV and V were given at:

Ninth Nordic Meeting on Clinical Physics, Gothenburg, Sweden, 15-17 June, 1977.

2nd Meeting of the European Group of Hyperthermia in Radiation Oncology, Rome, Italy, 19-20 September, 1980.

Symposium on Organ Blood Flow Measurements with Inert Gas Radiotracers, Kuopio, Finland, 21-11 May, 1981.

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1. INTRODUCTION

The medical usage of radioactive xenon has increased considerably during the last ten years. The clinical applications of xenon isotopes are lung function studies and measurements of organ blood flow. Although several xenon-isotopes are suitable for nuclear medical purposes, Xe-133 is by far the one most frequently used in clinical investigations.

Medical departments in Sweden purchased an estimated 5500 GBq (150 Ci) Xe-133 during 1980. More than half of this activity was used at two large hospitals in southern Sweden, geographically close to one another: the University Hospital of Lund, where extensive cerebral blood flow measurements are done, and the General Hospital in Malmö, where lung function studies are performed. Xenon isotopes are also used at these centres in a number of other medical research projects. It was thus clearly motivated to choose the physical and physiological aspects of xenon usage as the subject of this thesis.

Being an inert gas, xenon has certain qualities that differ from those of the more traditional radionuclides in use in nuclear medicine. In vivo, it is present in physical solution, chiefly in the body's water and fat, and does not participate in the biochemical reactions. It is freely diffusible and the blood-tissue gas exchange is therefore efficient and rapid. The solubility is, however, rather low and during a single lung passage, most of the xenon carried by the venous blood diffuses across the lung alveolar membrane and is exhaled. This property gives xenon the advantage of having a very short biological half-life, in the order of a few minutes. A small part dissolves, however, in fatty tissues and has a considerably longer biological half-life of about ten hours.

The short half-life of xenon in vivo introduces, on the other hand, also some drawbacks for its use in actual practice. Since most of the xenon is rapidly exhaled, proper handling and isolation of the radioactive gas must be carried out to prevent spreading it out in the laboratory atmosphere. It is still usually not actually possible to avoid leakage of xenon to the surroundings. This leakage emanates from equipment or parts that carry xenon, e.g loose face-masks, tubings etc. The patient is also a source of xenon isotope release to his surroundings. The staff working with xenon is therefore often exposed to radiation from both sealed xenon-sources, like spirometers, etc., and from air-borne xenon in the room-air.

The xenon isotopes generally give low absorbed doses per unit activity and several of them, including the dominating Xe-133, are classified in the group of least radio-toxical nuclides. This does not imply that precautions to hinder their spreading are unnecessary. Questions like room-air monitoring, ventilation of the laboratory, handling of the exhaled radioactivity, etc., are matters that must be considered when xenon isotopes are clinically used. The steps that are carried out to minimize the radiation hazard from xenon-usage are usually uncomplicated and can be as simple as the tightening of doors, installation of extra ventilation fans, etc. Usage of activated charcoal filter to trap the radioactive waste may also be advisable prior to direct release of xenon out-of-doors.

Patient investigations with xenon are usually performed with a scintillation camera or a multidetector set-up. The gamma₇ radiation of Xe-133 is of low energy, 81 keV, and compton scattering can therefore constitute a severe problem and reduce the signal-to-noise ratio. The volume and density of the organ being investigated affect the magnitude of scatter. The problem appears therefore to be greater for regional cerebral blood flow measurements (rCBF) than it is

for lung ventilation studies. rCBF-measurements are usually performed with a multidetector array where each detector views a regional part in one of the brain hemispheres. The rate of disappearance of the xenon isotope from each region is registered and taken as an index of the regional brain perfusion. Addition of signals from other parts of the brain due to compton scattering and hemispheric cross-talk obscures the regional signal and thus increases the uncertainty of the results. For several reasons, non-focusing, large-hole collimators are often used in non-invasive rCBF-measurements. Unfortunately, this further reduces the signal-to-noise ratio. In order to make correct judgements and interpretations of investigation-results obtained, it is important to be aware of the possible errors that can be introduced.

The indirect method to assess tissue blood-perfusion by measuring the rate of disappearance of xenon from the organ in study has several merits. Compared to many other methods, it is usually easy to carry out and can be repeated with short intervals. There are, however, also difficulties that must be considered before applying the method. The washout of xenon from the tissue being investigated is usually translated into blood-perfusion units. In order to do so, a mathematical model must be employed which, in itself, is a simplification of the actual circumstances. The results obtained from the calculations will therefore depend on the model being used. For each new research project where xenon isotope technique is planned to be used for assessment of tissue blood-perfusion, the reliability of the method and the suitability of the mathematical model used should first be carefully studied.

2. PURPOSE OF THE PRESENT STUDY

The research work on which this thesis is based consists of essentially two parts. The first part deals with some important practical aspects in the handling of radioactive xenon at a medical department:

- The alternative to direct release of exhaled xenon waste out-of-doors is to use xenon traps. In Paper I, the functional performance of activated charcoal traps for reclaiming of radioactive xenon waste is discussed.

- For the accelerator-produced Xe-127, recycling is a possible method to reduce the purchasing costs. A technique to recover the isotope is described in Paper II.

- Room-air monitoring of xenon-laboratories is advantageous in order to control the working environment for the staff. In Paper III, a simple and cheap monitor is introduced for continuous survey measurement of the room-air contamination.

A general discussion of these reports is given in Chapter 4.

The second part steps over from the field of radiation protection and handling of xenon isotopes to focus on some clinical applications of xenon isotopes.

- The effects of cross-talk and overlapping regions in regional cerebral blood flow measurements with Xe-133 in man are discussed in Paper IV.

- In Paper V, the applicability of the xenon washout technique for liver blood flow measurements on rat is discussed.

These topics are further presented and discussed in Chapter 5.

3. PROPERTIES OF XENON

3.1 Physical and Physiological Background

During the last decade of the 19:th century, several of the now known elements were discovered. In 1898, the British chemists Ramsay and Travers discovered three new rare gases in the residue left after evaporating liquid air components. The new members of the periodic table were given the names neon, krypton and xenon, taken from the Greek neos: new, kryptos: hidden and xenon: strange. It is an interesting coincidence that the name that element No. 54 of the periodic table was given at its discovery -the stranger- is quite a correct description of xenon's physiological qualities. In vivo, xenon (and even other rare gases) acts as a stranger and does not take part in any metabolic activity.

Molecular Weight	131.3
Boiling Point	-107.1°C
Solidification Point	-112°C
Density ($\rho_{\text{air}} = 1.3 \text{ g/dm}^3$)	5.9 g/dm ³
Specific Gravity (air = 1)	4.5

Table 3.1: Some physical constants of the element xenon.

The noble gases are generally monoatomic and until recently, it was believed that they do not form chemical compounds with other elements. During the 1960's and 1970's, several such compounds were, however, reported. A review of the chemistry of xenon has been published by Moody (1974). Some of the xenon compounds have a strong oxidizing ability and they have therefore found use in analytical chemistry as oxidizing agents. Xenon trioxide, for example, is highly

explosive and comparable with TNT while other xenon compounds, such as perxenates, can be handled as conveniently as most laboratory chemicals. Xenon compounds are achieved under extreme conditions and in the medical usage of xenon isotopes, such chemical reactions do not occur. In vivo, xenon associates, however, loosely with heme-proteins to form unstable complexes. Some physical constants of xenon are given in Table 3.1

Although the aggregational state of xenon under normal conditions is a gas, it is in varying degrees soluble in matter. In contact with a fluid or a tissue for example, a certain amount of the xenon diffuses into the new medium without forming -at least by currently accepted standards-, any chemical compounds with it; the xenon is said to be dissolved. An example of this process taken from daily routine at a nuclear medicine department is the contamination of rubber stoppers on xenon ampules. The solubility is specific for each medium and is usually expressed in terms of the Ostwald coefficient, L . It is defined as the ratio of the volume of the dissolved gas to that of the absorbing liquid or substance. If these are V_l and V_g , respectively, the solubility is $L = V_l / V_g$ (Markham and Kobe, 1941). Experimentally, the Ostwald coefficient L is usually determined by equilibrating the gas with the absorbing substance in a sealed test-tube. The equation of the Ostwald coefficient then becomes:

$$L = C_l / C_g$$

which is the ratio of the concentration of gas in liquid or dissolved phase and in the gaseous phase. The absolute uptake of xenon in a substance is thus a linear function of the partial pressure of the gas. This is in accordance with Henry's law, which says that the concentration of a dissolved gas is proportional to the partial pressure of the gas that is in gas-phase above the substance.

The Ostwald coefficient is independent of the partial pressure of the gas as long as gas-ideality remains. It is, however, dependent on the temperature and is a linear function of $\exp(1/T)$, where T is in Kelvin. The temperature at the determination must therefore be stated. A number of papers have been published concerning measurements of the Ostwald solubility for xenon, and a summary of these is presented in Table 3.2 (Yeh and Peterson, 1963,1965; Isbister et al., 1965; Veall and Mallet, 1965; Ladefoged and Anderson, 1967; Kitani, 1972). The high solubility in fat results in an accumulation of xenon in fatty tissue.

Substance	Ostwald Solubility
Water	0.083
Saline	0.085
Plasma	0.098
Red cells	0.200
Brain, grey matter	0.135
Brain, white matter	0.235
Fat	1.8

Table 3.2: Summary of average values of the Ostwald solubility for xenon in various substances.

In vivo, xenon is transported to and from the various tissues by the blood circulation. Another parameter is therefore essential to quantify the uptake of xenon in tissue: the partition coefficient λ . It is defined as the ratio, under equilibrium conditions, of the gas-solubility in tissue and blood, respectively:

$$\lambda = L_t/L_b$$

The dimensional units of λ vary in the literature between

(g blood/g tissue) and (ml blood/g tissue), i.e. with the blood component specified as a mass- or a volume-concentration. Although confusing at first sight, the two concepts are virtually equal, because the density of blood is essentially 1 g/ml. The Ostwald solubility for xenon is, as already mentioned, sensitive to the temperature in such a way that a rise in the temperature generally results in a reduced solubility. The partition coefficient appears to be less sensitive to changes in the temperature (Andersen and Ladefoged, 1967). It is, however, dependent on the blood-hematocrit, which is due to the relatively high solubility of xenon in the red cells. Table 3.3 summarizes values of the partition coefficient found in the literature for various tissues (Andersen and Ladefoged, 1967; Veall and Mallet, 1965; Isbister et al., 1965; Conn, 1961).

Tissue	Partition coefficient λ (ml/g)
Brain, grey matter	0.8
Brain, white matter	1.5
Liver	0.7
Kidney	0.7
Fat	8.0 - 14.0

Table 3.3: Summary of mean values of the partition coefficient of xenon in various tissues. The values are dependent on several factors and therefore only tentative.

A large tissue-solubility usually accounts for a high content of fat in the tissue. Conn found in 1961 that the increased solubility of xenon in red cells was caused by a xenon-hemoglobin association. Conn investigated the cause of this attraction and proposed a semi-solubility explanation of the phenomenon, including adsorptive Van der Waal-interactions or clathrate formation between xenon and hemoglobin. Schoenborn (1965) later published new and in-

teresting data on xenon's binding to hemoglobin based on X-ray diffraction analysis. Schoenborn localized the binding sites of xenon in horse hemoglobin in both the α - and the β -chains and made a tentative suggestion that the closest neighbours to a xenon atom were the amino-acids valine, leucine and phenylalanine. The author suggested that this chemical complex was stabilized by dipole- and quadrupole moments.

3.2 Medical Applications

Administration of xenon in vivo is usually performed by inhalation of xenon gas or by injection of xenon-solution into the blood stream or directly into the parenchyma of the organ in question. Inhalation of xenon results in a blood-uptake due to diffusion of xenon across the lung-alveolar membrane. The concentration of xenon in the arterial blood from the lungs is then the Ostwald coefficient multiplied by the concentration of xenon in the alveolar-air. For a blood-hematocrit of 50%, the arterial blood-concentration is about 15% of that in the lungs.

Xenon is, with few exceptions, distributed to the organs by the arterial blood circulation. The uptake of xenon in the tissue is, according to Fick's principle, dependent on the blood flow. The theoretical principles for blood flow measurements by using freely diffusable agents were formulated by the Kety-group (Kety and Schmidt, 1945, 1948; Kety, 1951, 1960). The method was further developed for regional cerebral blood flow measurements (rCBF) with Kr-85 (Lassen and Munck, 1955; Lassen and Ingvar, 1961) and, later, with Xe-133 (Ingvar et al., 1965). In these basic works, the isotopes were administered by intra-carotid injection. Through the research done by Mallet and Veall (1965), Veall and Mallet (1966), Risberg et al. (1975), Obrist et al. (1975), Kuikka et al. (1977), and Kanno and

Lassen, (1979), among others, non-invasive methods to measure rCBF have been developed. The method has also been in extensive use for studies of the blood flow in a number of organs, such as the liver (Rees et al., 1964; Darle, 1970; Gelin et al., 1978) and the kidney (Thornburn et al., 1968).

The other important medical application of radioactive xenon is for charting the lung-ventilation in patients with pulmonary disease. This technique has been in use since the mid- 1950's (Knipping et al., 1955). The isotope is usually mixed with air in a closed spirometer system and inhaled by the patient for a couple of minutes. Registration of the spatial distribution of the isotope in the lungs, e.g. by a scintillation camera or a multidetector arrangement, can then show the regional ventilation of the lungs. The functional status and volumes of the lungs can further be determined by using a specific breathing technique (Ball et al., 1962; Jacobstein, 1978; Bunow et al., 1979). Lung perfusion can also be determined by an intravenous injection of xenon while the patient holds his breath. A scintillation-camera image of the corresponding isotope distribution in the lungs shows the degree of regional perfusion.

About 90% of the amount of xenon that is used during a medical examination is exhaled by the patient within the first ten minutes after the investigation is terminated. The major sources of this rapid washout are from xenon remaining in gaseous phase in the lungs and from xenon which is dissolved in the blood and highly perfused organs. The remaining 10% of xenon in vivo is dissolved in muscles and fatty tissues. Using data presented by the Brookhaven group, clearance from muscles takes place with a biological half-life of about 0.5 hours (Susskind et al., 1977). Washout from fat is much slower, which is due to the high xenon-solubility and low blood-perfusion in such tissue. The Brookhaven-investigation reported two different rates of

washout from fatty tissue with average biological half-times of 2.7 and 10.5 hours, respectively.

The amount of xenon activity which is being used and exhaled during a single medical investigation differs with the type of investigation carried out. For rCBF-investigations where Xe-133 is administered by inhalation or by an i.v. injection, the amount of activity used may be 1 GBq or more. For lung ventilation studies with a scintillation camera, around 500 - 700 MBq of Xe-133 is used. Use of Xe-127 reduces the activity required by a factor of about 3 (Hoffer et al., 1973). It is obvious that direct release of these activities into the laboratory air is unacceptable from the standpoint of radiation safety. Several techniques to isolate the exhaled gases from the room-air have therefore been employed. These aspects are further discussed in Chapter 4.

It is well-known that xenon has anesthetic side-effects if it is inhaled at high partial pressures (greater than 0.2 atm). Clinical signs are descending depressions of the central nervous system, muscle relaxation etc. (Collins, 1976). Upon termination of xenon inhalation, these effects cease within a few minutes. Cullen and Gross (1951) reported the successful use of a mixture of xenon (80%) and oxygen (20%) for anesthetizing two patients during surgical operations. No anesthetic effects have, however, been reported for the ultra-low partial pressures in current use in nuclear medicine.

The possibility to utilize stable xenon gas as an X-ray contrast medium in conjunction with CT-scanning imaging has been discussed in recent years, mainly for measurements of local cerebral blood flow (LCBF). The technique is essentially based on the clearance of xenon from brain tissue measured by repeated brain scannings (Kelcz et al., 1978; Meyer et al., 1980). High partial pressures of xenon must

be used and anesthetic side-effects usually therefore occur. In contrast to the radioactive xenon technique, this new approach offers high spatial resolution and determination of individual partition coefficients in different tissue-compartments. The time-lapse of xenon washout can, however, not be followed accurately due to limitations in the scanning speed of CT-scanners. The radiation dose is typically about 20 times higher than for a corresponding CBF-investigation with radioactive Xe-133 (Kelcz et al., 1978).

3.3 The Xenon Isotopes

The element xenon has nine stable isotopes and about twenty-five that are radioactive. Of the latter, at least five have properties which make them suitable for medical diagnostic usage: Xe-123, Xe-125, Xe-127, Xe-133 and Xe-135 (see Table 3.4).

Isotope	Type of decay	Half-life	Major gamma-energies: approximative energies (MeV) and intensities
^{123}Xe	EC, β^+	2.08 h	0.149 (49%), 0.178 (15%)
^{125}Xe	EC, β^+	17.0 h	0.188 (55%), 0.243 (29%)
^{127}Xe	EC	36.4 d	0.172 (25%), 0.203 (68%), 0.375 (17%)
^{133}Xe	β^-	5.25 d	0.081 (37%), Cs X-rays: 0.031 - 0.035
^{135}Xe	β^-	9.09 h	0.250 (90%)

Table 3.4: Summary of radioactive xenon isotopes suitable for nuclear medicine applications (from Table of Isotopes, Lederer and Shirley, Eds., 1978).

Due to manufacturing and distributional reasons, Xe-133 has, however, become by far the most commonly used noble gas tracer and is presently responsible for more than an estimated 99% of the total global medical consumption of radioactive xenon. It is obtained as a fission product after neutron bombardment of U-235, and is extracted from the irradiated uranium at high temperature (McLain, 1973). Alternatively, it can be produced by direct neutron-irradiation of stable Xe-132 (Riezler, 1943). It decays by beta-emission to the stable nuclide Cs-133 (cesium) with a physical half-life of 5.3 days. About 99% of all decays occur to a short-lived excited state (6 ns), 81 keV above the ground state of Cs-133. Gamma-emission at 81 keV follows in about 37% of all the decay events. A significant number of the Cs-daughter nuclei are de-excited by internal conversion, which leads to the emission of characteristic X-rays at 31-35 keV.

During the last decade, the use of another xenon-isotope, Xe-127, has won increased interest, especially for lung ventilation studies (Hoffer et al., 1973; Atkins et al., 1977). It is presently routinely produced at Brookhaven National Laboratories, Upton, New York, by irradiating stable cesium with 100-200 MeV protons according to the reaction: $\text{Cs-133}(p,2p5n)\text{Xe-127}$. There are also plans for production at other accelerator-centres in the future. It decays by electron capture (EC) to stable iodine, I-127, with a half-life of 36.4 days. Figure 3.1 shows the principal types of decay for both Xe-133 and Xe-127. The corresponding pulse-height distributions of the photon-emission, obtained with Germanium-detectors, are shown in Figure 3.2.

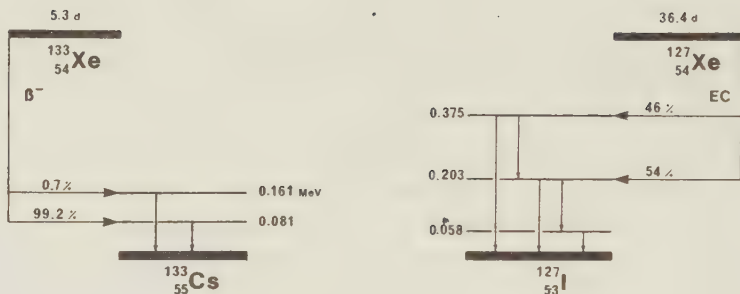


Figure 3.1: Decay scheme of Xe-133 and Xe-127.

The dominating gamma-energies of Xe-127, 172 and 203 keV, respectively, are better suited for the Anger-camera than the 81-keV-radiation from Xe-133. Unfortunately, the gamma-spectrum of Xe-127 also contains 375 keV-photons, which limits the choice of suitable scintillation camera-collimators to those with thick lead-septas. Figure 3.3 demonstrates scintillation camera images of a Xe-127 point-source with two different collimators, 140 keV fine hole and 360 keV coarse hole, respectively. The energy-window was 30% above the 203 keV peak. Septum-penetration of the 375 keV photons is responsible for the visible star-pattern with the low energy collimator. The corresponding pulse-height distributions from the camera reveal the excessive penetration of 375 keV gamma-radiation.

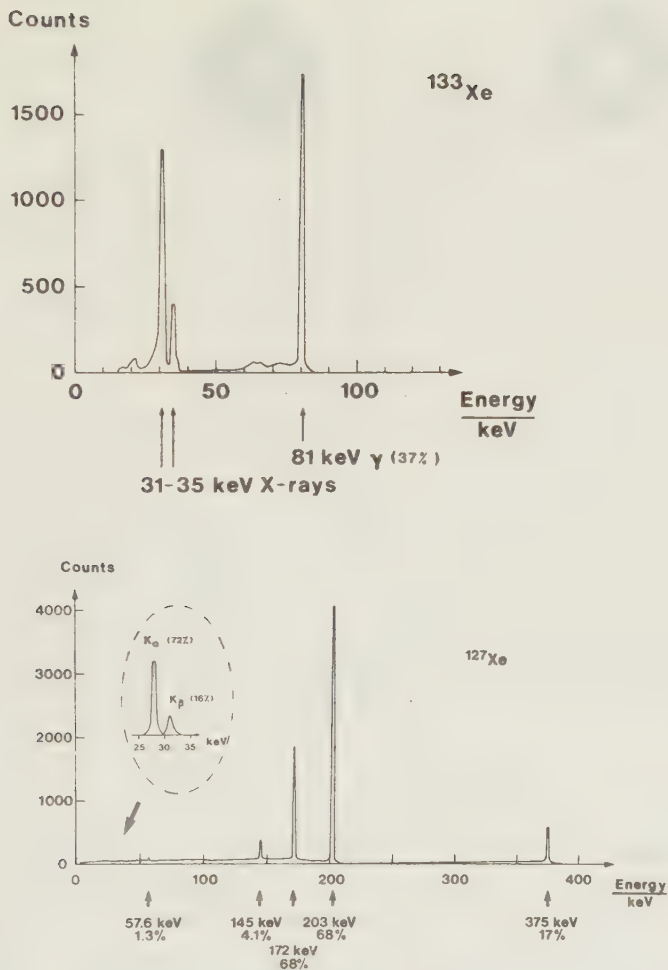


Figure 3.2: Pulse-height distributions of the photon emission from Xe-133 (top) and Xe-127 (below). An intrinsic Ge-detector was used to measure Xe-133 and the characteristic X-ray emission (iodine) from the decay of Xe-127. The gamma-radiation from Xe-127 was measured with a Ge(Li)-detector.

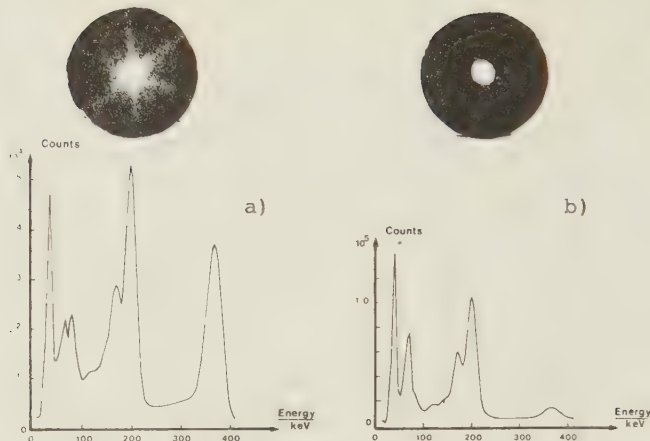


Figure 3.3: Pulse-height distribution of Xe-127 obtained with a gamma-camera provided with two types of collimators. The septum-penetration of the 375 keV gamma radiation is clearly demonstrated in Figure a) (140 keV collimator, 12,000 holes) and causes the starpattern in the image of a Xe-127 point-source. The corresponding image with a 360 keV collimator (1,000 holes) is shown in Figure b).

The remaining xenon-isotopes listed in Table 3.4 have only rarely been used in nuclear medicine and are not presently produced regularly as radiopharmaceuticals. A few lung ventilation studies have been reported using Xe-135 (Newhouse et al., 1968). It is, as for Xe-133, produced by uranium-fission, and decays by beta-emission to Cs-135 (Fritz and Robertson, 1968; McLain, 1973). Its dominating gamma-energy is 250 keV. Its short half-life, 9 hours, makes difficult demands on the manufacturer for its distribution to hospitals. The daughter nucleus, Cs-135, is radioactive, but its half-life is 3 million years, so it is of low risk for the environment.

Xe-125 was proposed by Hines et al. (1975) as an alternative for Xe-127 due to a better productional yield. The authors suggested a productional process in which Xe-125

was formed by irradiation of stable iodine according to the reaction: $I-127(p,3n)Xe-125$. The decay is by electron capture to $I-125$ - a well-known radionuclide in nuclear medicine. The major gamma-energies of $Xe-125$ are 188 and 243 keV, respectively. The half-life, 17 hours, is rather short and fast distribution to the hospitals is therefore mandatory. The daughter nuclide, $I-125$, will probably metabolize and concentrate in the thyroidea and thus give a small additional radiation dose to the patient.

$Xe-123$ also decays by electron capture to another well-known iodine-isotope: $I-123$. This latter isotope is often produced by irradiating stable iodine with 50 - 60 MeV protons according to the reaction: $I-127(p,5n)Xe-123$ (Fusco et al., 1972, Mattsson et al., 1976). Due to the very short half-life of the xenon so produced (2 hours), it is transformed to $I-123$ during the subsequent transportation to the hospitals unless a very quick delivery is made. If $Xe-123$ is to be used clinically, its daughter, $I-123$, will probably also concentrate in the thyroidea. The additional radiation dose will, however, be very low due to the low-dose properties of $I-123$ (MIRD, 1975).

Hines et al. (1975) calculated the detectable number of photons for a scintillation camera per disintegration from each of these five xenon-isotopes. They found that $Xe-127$ gave the best detectable yield per disintegration: about a factor 1.5 better than for $Xe-125$, $Xe-123$ and $Xe-135$, and a factor 3 better than for $Xe-133$. The remaining radioactive xenon isotopes are characterized by either very short half-lives or by very low gamma-emission yields, and they have thus not yet been studied.

3.4 Radiation Exposure and Dosimetry

Because xenon is a gas, some special contamination situations frequently occur that are rarely seen with other radionuclides in nuclear medicine. Leakage into the laboratory air from the equipment and the patient is often difficult to avoid (Rummerfield et al., 1971; LeBlanc and Johnson, 1975; Bolmsjö, 1981). The staff and patients are therefore exposed to radiation from three sources:

- 1.) By radiation emanating from patient and equipment,
- 2.) by xenon released into the surrounding laboratory air, and
- 3.) by xenon inhaled and dissolved in vivo.

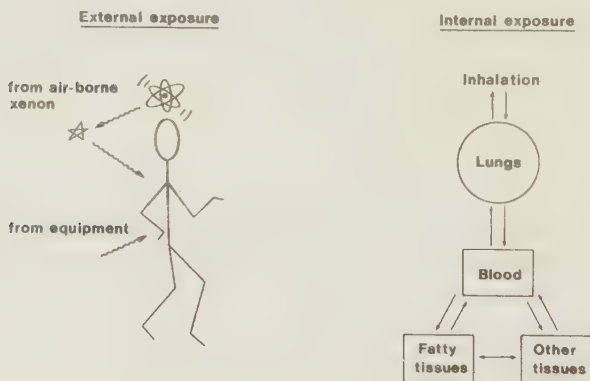


Figure 3.4: The radiation environment in a laboratory where radioactive xenon is used.

For the staff, the external exposure (paragraphs 1. and 2. above) is several orders of magnitude larger than the internal exposure (paragraph 3). This is because the tissue-concentration of xenon is, due to the low solubility of xenon, less than the surrounding air-concentration (ex-

cept for fatty tissue), and it can therefore not be a major source of radiation exposure. For the patient, the opposite is true and the dose contribution from internal exposure dominates. Absorbed dose according to paragraph 2 above, is calculated by assuming that a standard man is submersed in a semi-infinite and homogenous mixed xenon-cloud. Radiation equilibrium exists at all points of such a cloud and the further calculations are therefore somewhat simplified, since the absorbed dose must equal the energy of the radiation emitted per unit mass, in order to conserve energy. Persons working in xenon-contaminated atmospheres inhale xenon, which is then distributed throughout the body. Due to the rather low solubility of xenon in blood, the equilibrium tissue concentration of xenon will only be about 10 - 20% of the corresponding air-concentration in the lung-alveolas, except for fatty tissues, where the concentration is of the same order as in the lungs. The internal dosimetry of xenon isotopes due to this uptake has been calculated by several researchers: by Lassen (1964), and Loken et al. (1970) among others. The latest reports of xenon dosimetry are those of Goddard and Ackery (1975) and Atkins et al. (1980). Both of these are based on calculations in accordance with the MIRD-concept, a method that utilizes Monte Carlo-simulated transport of radiation in vivo. The report of Atkins et al. is an official MIRD-report.

Recommendations on radiation protection matters are issued by the international organization ICRP - International Commission on Radiological Protection. These recommendations have been adopted and are in use in most countries. A general rule is that all exposure to ionization radiation should be kept as low as possible.

The individual's occupational exposure to ionizing radiation must be limited so that the three conditions 3.1 - 3.3 below of the yearly dose equivalent H are all satisfied:

$$\sum_T w_T \cdot H_T \leq 0.05 \text{ Sv} \quad \text{as YC} \quad (3.1)$$

$$H_T \leq 0.5 \text{ Sv} \quad (3.2)$$

$$H_{\text{lens}} \leq 0.15 \text{ Sv} \quad (3.3)$$

where w_T is a weighting factor for tissue T and defined in ICRP Publication No. 26. H_T and H_{lens} are the yearly dose equivalent in tissue T and the lens of the eye, respectively. Condition 3.1 limits the hazard for stochastic or late effects of radiation exposure, that is induction of cancer and genetic damage. The factor w_T in 3.1 expresses the relative sensitivity to such damage for each individual organ. The other two conditions, 3.2 and 3.3, limit the risks for inducing non-stochastic (acute) effects on the organism. For non-occupational exposure, the absolute upper limit of the dose-equivalent is one-tenth of the values given above.

Occupational exposure from airborne xenon isotopes must be limited so that the conditions 3.4 - 3.6 below are satisfied.

$$\sum_T w_T \cdot \dot{H}_T \cdot fC(t)dt \leq 0.05 \text{ Sv} \quad (3.4)$$

$$\dot{H}_T \cdot fC(t)dt \leq 0.5 \text{ Sv} \quad (3.5)$$

$$\dot{H}_{\text{lens}} \cdot fC(t)dt \leq 0.15 \text{ Sv} \quad (3.6)$$

where $C(t)$ is the concentration of the radionuclide at any time t (Bq/m^3). The integrations are over a working year (2000 h). $\dot{H}_T$ and $\dot{H}_{\text{lens}}$ are the dose equivalent rate in any tissue T and the eye lens, respectively ($\text{Sv} \cdot \text{m}^3 \cdot \text{Bq}^{-1} \cdot \text{h}^{-1}$). It must be emphasized that the conditions 3.1 - 3.3 are the overriding limits and must be applied if exposure from other sources occurs.

The concept MPC -Maximum Permissible Concentration- was earlier used to express the concentration of a radionuclide in air or water that resulted in maximally permitted dose-equivalent. A number of MPC-values for different radionuclides were published in ICRP Publication 2 (1959). New data on the radiation sensitivity of each organ have necessitated a recalculation of the older limits. The MPC-concept has now been replaced by two new concepts, ALI - Annual Limit on Intake, and DAC - Derived Air Concentration (ICRP Publication No. 30, Part 1, 1979). For xenon, DAC has the same implication as the older MPC, i.e. it expresses the mean air concentration which, after spending one working year (2000 h) in such an atmosphere, gives maximal permitted dose equivalent according to the conditions 3.4 - 3.6. In the recalculations of the maximal air-concentrations, it was found that the older MPC-values for xenon were too pessimistic and the new upper limits are about 10 times higher. Table 3.5 summarizes the present values of DAC for the five most interesting xenon isotopes. The difference between DAC in a semi-infinite xenon cloud compared to a finite room is due to corrections for the lack of radiation equilibrium in the latter case. In actual practice, the yearly average air-concentration of xenon in a nuclear medicine laboratory must be lower than is stipulated by DAC, since xenon usually is not the sole source of exposure for the staff.

Radionuclide	Semi-infinite cloud	1000 m ³ room	500 m ³ room	100 m ³ room
¹²³ Xe	2·10 ⁵	5·10 ⁶	6·10 ⁶ *	6·10 ⁶ *
¹²⁵ Xe	6·10 ⁵	1·10 ⁷	1·10 ⁷	2·10 ⁷
¹²⁷ Xe	5·10 ⁵	1·10 ⁷	1·10 ⁷	2·10 ⁷
¹³³ Xe	4·10 ⁶	2·10 ⁷ *	2·10 ⁷ *	2·10 ⁷ *
¹³⁵ Xe	5·10 ⁵	4·10 ⁶ *	4·10 ⁶ *	4·10 ⁶ *

Table 3.5: Derived Air Concentration (DAC) in Bq/m³ for Xe-123, Xe-125, Xe-127, Xe-133 and Xe-135. The values are for exposure during one working year (2000 hours). For the *marked values, the skin-dose limits the maximally permitted exposure (condition 3.5). For the others, the condition (3.4) limit the exposure. (From ICRP Publication 30, Part 2, 1980)

The patient dose is almost entirely determined by the internal exposure. Tables 3.6 and 3.7 summarize the absorbed dose calculations taken from the reports of Goddard and Ackery (1975) and Atkins et al. (1980) (adjusted to represent equal conditions). The latter report takes into account experimentally determined retention-data of xenon in vivo. The discrepancies between the two reports are very small. The tables can be approximately converted linearly to other xenon-concentrations and administration times. For an accurate conversion, the user should, however, consult the original reports.

Organ	Absorbed dose (mGy):					
	^{125}Xe		^{127}Xe		^{133}Xe	
	Goddard	Atkins	Goddard	Atkins	Goddard	Atkins
Lung	0.28	-	0.28	0.36	0.65	0.82
Red marrow	-	-	-	0.13	-	0.12
Blood	0.02	-	0.02	-	0.06	-
Gonads	0.08	-	0.08	0.09	0.06	0.10
Fat	0.15	-	0.15	-	0.41	-
Major airway mucosa	2.30	-	1.32	-	10.70	-
Total body	-	-	-	0.10	-	0.11
Thyroid	0.5	-	-	-	-	-

Table 3.6: Absorbed dose (mGy) in various organs from the inhalation of xenon from a spirometer during 5 minutes. Zero activity in the lungs is assumed at the start of inhalation. Equilibrium concentration in the lungs is assumed to be 37 MBq/l (1 mCi/l). The dose contribution to the thyroid is due to the fact that Xe-125 decays to I-125. About 1.5 kBq of I-125 is formed in vivo and if all this activity is metabolized, the absorbed dose to the thyroid is about 0.5 mGy. Goddard-Ackery gave the value 15 mGy, but they included extra contributions from the injection of 37 MBq Xe-125 (i.v.) and a further single inhalation of 37 MBq of Xe-125.

Organ	Absorbed dose (mGy):					
	^{125}Xe		^{127}Xe		^{133}Xe	
	Goddard	Atkins	Goddard	Atkins	Goddard	Atkins
Lung	0.02 (0.15)	-	0.02 (0.15)	0.03	0.05 (0.40)	0.07
Red marrow	-	-	-	0.01	-	0.01
Blood	0.03 (0.22)	-	0.03 (0.22)	-	0.11 (0.82)	-
Gonads	0.003 (0.02)	-	0.003 (0.02)	0.01	0.001 (0.01)	0.01
Fat	0.007 (0.05)	-	0.007 (0.05)	-	0.01 (0.10)	-
Major air- way mucosa	0.04 (0.57)	-	0.02 (0.34)	-	0.19 (2.57)	-
Total body	-	-	-	0.01	-	0.01

Table 3.7: Absorbed dose in various organs from intravenous injection of 37 MBq of xenon. The injection volume is 10 ml and the transportation of the activity to the lungs is assumed to take 10 seconds. The patient holds his breath for 0.5 minutes in conjunction with the injection. Washout from the lungs is assumed to occur with a half-time of 21.7 seconds after the apnea period. The values between the brackets are for the case of very low ventilation rate of the lungs ($t_{1/2} = 5$ minutes).

4. HANDLING OF XENON ISOTOPES: CONTAMINATION, TRAPPING AND MEASUREMENT

4.1 Atmospheric Contamination

Direct release of xenon to the outdoor atmosphere is a commonly used method to get rid of the radioactive waste, especially if the frequency of medical investigations with xenon is small. The method is simple but careful consideration of the possible pathways for the released xenon gas is necessary so that unwanted intake of activity through open windows, fan inlets etc. is avoided. The method has been used now and then at the University Hospital of Lund in conjunction with rCBF-investigations and lung ventilation studies. About 30 GBq of Xe-133 per week has maximally been released to the atmosphere.

An estimation of the average air-concentration of xenon at different distances in the wind direction from the source of release can be made by using the well-known plume-equation (Slade, 1968):

$$\bar{X}(x,y) = \frac{Q}{\pi \cdot \sigma_y \cdot \sigma_z \cdot u} \exp\left\{-\left(\frac{y}{2\sigma_y}\right)^2 + \left(\frac{h}{2\sigma_z}\right)^2\right\}$$

where

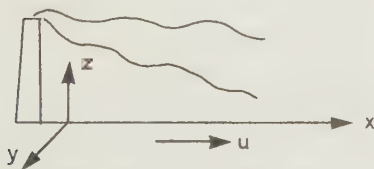
$\bar{X}(x,y)$ = the average concentration (Bq/m³) down-wind at ground level

Q = source strength (Bq/s)

σ_y, σ_z = dispersion coefficients for the activity in a plume in the y- and z- directions (m)

u = the mean wind speed (m/s)

h = effective height of the source above the ground (m)



Even if the release of radioactive xenon is carried out on the top of a hospital building, the effective height of the release is virtually zero because turbulences caused by large buildings may draw the xenon gas down to the ground. Using data from Slade (1968), Table 4.1 gives the dilution of a release at different distances from the source in the wind direction. The data are given for neutral weather conditions and the values vary with a factor of 10, either higher or lower than the stated values, for other types of weather.

Wind Speed (m/s)	Dilution coefficient (s/m^3)			
	Downwind distance			
	10	100	1000	10000
1	0.8	$0.8 \cdot 10^{-2}$	$1.3 \cdot 10^{-4}$	$3.5 \cdot 10^{-6}$
5	0.16	$0.16 \cdot 10^{-2}$	$2.6 \cdot 10^{-5}$	$7 \cdot 10^{-7}$
10	0.08	$0.8 \cdot 10^{-3}$	$1.3 \cdot 10^{-5}$	$3.5 \cdot 10^{-7}$

Table 4.1: Ground level dilution coefficients at different wind speeds and distances from the source (effective height = 0). The values must be multiplied with the source strength (Bq/s) to obtain the concentration (Bq/m^3) at the point in question (from Slade, 1968).

If the daily (8 hours) release of a xenon isotope is 5 GBq (174 kBq/s) and the wind speed is 5 m/s, the estimated average concentration at different distances from the source is (Table 4.2):

Downwind distance from the source (m)	Average concentration of xenon (Bq/m^3)
10	$3 \cdot 10^4$
100	$3 \cdot 10^2$
1000	5
10000	0.1

Table 4.2: Average concentrations of xenon at different distances from the source (down-wind) at an assumed release of 174 kBq/s.

Although these data are theoretical and must be used with discretion, they give a useful estimation of the activity concentrations that can be expected in the surroundings due to atmospheric release of radioactive xenon. In a previous study of hospital releases of Xe-133 to the atmosphere, the concentration 30 m down-wind from the outlet of a rCBF-laboratory in Lund was measured, see Table 4.3 below (Bolmsjö, 1981).

Activity release	Wind speed	Mean air concentration 30 m from the source
3 GBq (during 6 h)	1 m/s	0.74 kBq/m ³
1,5 GBq (during 3 h)	5 - 10 m/s	3.4 kBq/m ³

Table 4.3: Measured activity of Xe-133 outside a medical xenon-laboratory. The results are in reasonably good agreement with the theoretical values obtainable from Table 4.1.

The quick atmospheric dilution of discharged xenon implies that the absorbed dose to individuals from daily releases of Xe-133 in the order of 5 GBq, is negligible except very close to the source. Because a large number of people normally work or live in the surroundings close to a hospital, the collective dose should, however, be considered. By using Tables 3.5 and 4.1, an estimation of the maximal collective dose equivalent can be made. If 10000 individuals are exposed by the plume in an area up to 10 km from the source, daily releases of 5 GBq (174 kBq/s) of Xe-133 should not likely give a weighted collective dose equivalent in excess of 10^{-2} man·Sv per year and probably be one or two orders less. Release of any of the other four xenon isotopes listed in Table 3.5 gives a maximum dose equivalent of about one order higher magnitude. The collective dose due to direct release of xenon isotopes is thus normally quite small. The risk of the gas re-entering the building through open windows or room-ventilation intakes must, however, be taken into consideration. If this happens, unnecessary radiation

exposure of personnel and others occurs. Xenon traps then constitute a practical and cheap solution for reclaiming of the radioactive waste.

It could be interesting to compare hospital release of Xe-133 with the discharge of Xe-133 from the Swedish nuclear power plant at Barsebäck (boiling water reactor, BWR, 1100 MW). The plant released about 1500 GBq of Xe-133 to the atmosphere during 1980. During the same time, the hospital consumption of Xe-133 in Lund was nearly twice that activity. Since charcoal traps usually were used, only a minor part of that activity was discharged to the atmosphere. An interesting report on the release of radioactive noble gases from nuclear power stations has been published by Kolde et al. (1973).

Of general interest are the results from two studies concerning the global atmospheric contamination of Xe-133. Kuntz and Paperiello (1976) measured the air-concentration of Xe-133 in the state of New York and found it to be of the order of 0.1 Bq/m^3 . They ascribed this contamination to releases from BWR nuclear plants located in the north-eastern United States. An earlier study by Scholch et al. (1966) reported an average Xe-133 concentration of 0.004 Bq/m^3 in the Federal Republic of Germany. The source of this activity is not fully understood, but correlated in time with a Chinese nuclear bomb test.

4.2 Trapping of Xenon Isotopes

An advantageous alternative to direct release of the xenon isotope waste is to connect the patient to a xenon trap during the first 5 - 10 minutes after completion of the medical investigation. During these few minutes, the exhaled air is pumped through an activated charcoal filter in which the xenon is adsorbed and trapped. The exhaled air is

thus decontaminated from the radioactive xenon gas.

Physical adsorption of xenon on activated charcoal can be regarded as a condensation of the gas on the charcoal's surface. The binding forces are, however, rather weak and the xenon is therefore not permanently trapped. A continuous exchange between adsorption and desorption of xenon atoms thus occurs. The atoms that are temporarily desorbed (i.e. are freed), are carried forward by the exhaled air pumped through the trap until they are again adsorbed. By this process, xenon atoms slowly progress through the trap and after some time reach the effluent side where the final release occurs. The design of xenon traps should thus preferably be carried out so that the residence time of the isotope in the trap is long enough to allow for a substantial radioactive decay before the break-through occurs.

Activated charcoal filters were first developed for use in the nuclear power industry to minimize the release of radioactive fission products (Keilholtz, 1971). For medical purposes, xenon traps have been used over the last ten years and there are several manufacturers of these devices at present. Although some papers have been written concerning medical xenon traps, very little has been published concerning their functional performance and properties in actual practice. An investigation of xenon traps for clinical use was therefore made and is described in Paper I of this thesis.

Results

Trapping of xenon isotopes on activated charcoal was found to be an effective method to isolate exhaled radioactive xenon waste. Virtually all xenon could effectively be removed from the exhaled air. The adsorption capacity of charcoal was, however, found to be deteriorated by moisture present in the exhalation air. Drying of the exhaled air

was therefore necessary prior to passage through the trap. The carbon dioxide present in the exhalation air was found to reduce the trapping capacity by 25%. The use of carbon-dioxide drying agents was not, however, found to be mandatory.

Two commercially available charcoal traps were tested. They were found to work satisfactorily at room temperature for approximately 20 patient investigations, where 100 litres of exhaled air were collected and pumped through the trap during each patient investigation. After that point, substantial break-through of xenon occurred. Taking the decay of the xenon isotope into consideration, the capacity of these two units was found to be satisfactory for centres where the frequency of investigations with xenon isotopes is low.

Refrigeration of a charcoal trap at -20°C was found to improve the running time of a charcoal trap considerably before break-through of the xenon occurred. Even with very high patient frequency (up to 11 investigations a day), the residence time of Xe-133 in the trap was long enough to permit substantial decay of its activity. Refrigerated traps are thus the best choice for clinics with a high rate of patient investigations with xenon isotopes.

4.3 Recycling of Xenon Isotopes

The possibility to re-use xenon isotopes after a medical investigation was discussed by several research groups during the 1970's (Vaalburg et al., 1971; Forouzan-Rad, 1976). Basically, the question is an economic issue and became of interest when accelerator-produced Xe-127 was made available in the mid-1970's. The long physical half-life of Xe-127 (36.4 days) makes it theoretically possible to reprocess the isotope without any large losses due to physical decay.

This question was discussed in Malmoe and Lund during the mid 70's in conjunction with an eventual change from Xe-133 to Xe-127 for lung function studies. There was also interest in the projected plans for reprocessing Xe-133. From the initial discussions, a project was started with the ultimate goal of developing a small-scale xenon reprocessing system suitable for medical purposes. Paper II in this thesis is the scientific report from that project.

Recycling of xenon isotopes in medical clinics can be divided into two steps:

- 1) trapping of the exhaled xenon from previous patient investigations, and
- 2) release and collection of the trapped xenon.

Step 1 above is preferably done by adsorption on activated charcoal as described in Paper I. The second step to release the trapped xenon is most easily achieved by heating the charcoal to high temperature at which the xenon atoms are no longer bound to the charcoal. By blowing a small volume of nitrogen gas through the trap, the xenon isotope is carried out of the trap and can be collected.

Results

Recycling of xenon isotopes by the proposed model was found to function well and with high efficiency. Virtually all the xenon collected could be recovered in about 5 litres of nitrogen.

The usefulness of the method for clinical applications has not yet been fully explored. For the method to be of significant importance in the handling of Xe-133, very large amounts of activity must be used in order to justify its use

from an economic point of view. The medical interest that has been focused on Xe-127 for lung ventilation studies has not yet lead to a wide clinical usage of this isotope.

The new and promising development made by the Copenhagen rCBF-group to measure 3-dimensional cerebral blood-flow by using a fast scanning SPECT-system (single photon emission computerized tomography), may eventually reveal further applications for Xe-127 (Kanno and Lassen, 1979; Stokely et al., 1980; Lassen, 1981). Rather large amounts of activity are needed for this application and if Xe-127 is to be routinely used, recycling is likely to be necessary, for purely economic reasons.

4.4 Measurement

Leakage of xenon from the patient and the set-up is usually unavoidable. Room-air monitoring of the airborne activity in the laboratory is therefore advantageous to ensure a proper working environment for the staff. If $C(t)$ is the concentration of xenon in the air at any time t , the mean concentration $\overline{C(t)}$ during a year is:

$$\overline{C(t)} = \frac{\int C(t) dt}{\int dt}$$

For occupational exposure, the condition $\overline{C(t)} < 1$ DAC must be fulfilled.

Continuous measurement of xenon leakage is usually performed by pumping room air through an open ionization chamber which is shielded from external radiation. The ionization current is then proportional to the activity concentration in the room-air. Instruments based on this or similar techniques usually have a least detectability for Xe-133 of around 0.05 - 0.1 MBq/m³. Taking the new DAC-values for Xe-133 into consideration (4 - 20 MBq/m³), a least detect-

able activity of a survey meter of 0.4 MBq/m^3 ($1/10 - 1/50$ of DAC) is, however, acceptable in many situations.

In Paper III, a simple and cheap instrument for continuous measurement of airborne Xe-133 in the laboratory is discussed. The instrument was constructed by mounting a GM-tube inside a small charcoal filter and continuously pumping air through it. The unit was field-tested during five months at a rCBF-laboratory in Lund.

Results

The Xe-133 monitor was found to function well in the clinical situation and accurately recorded the activity leakages. Several simultaneous measurements were performed with an ionization-chamber system and the correspondance between the two detectors was very good. The least detectable concentration was less than 0.4 MBq/m^3 . By replacing the GM-tube with a NaI-scintillation detector, the sensitivity was enhanced to 50 kBq/m^3 . Figure 4.1 shows a typical recording of activity leakage during a working day at the rCBF-laboratory.

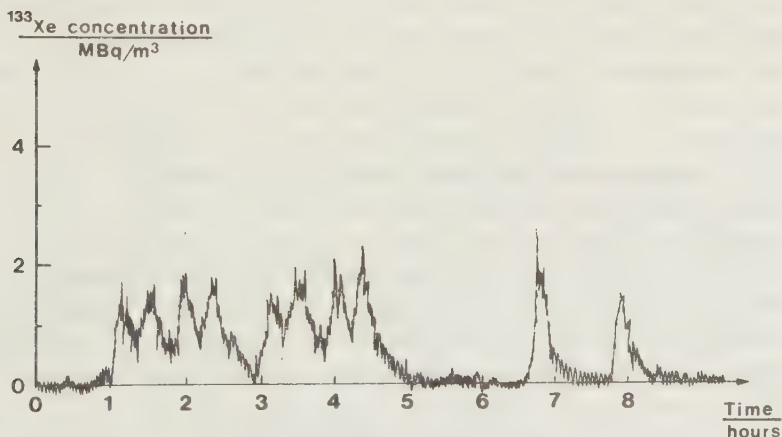


Figure 4.1: The concentration of Xe-133 in rCBF-laboratory in Lund during a working day. 0.7 GBq was used for each patient-investigation. The peaks represent the leakage of activity at each investigation. The diagram was obtained 1.5 m from the patient.

4.5 Discussion and Conclusions

Atmospheric releases of radioactive xenon from nuclear medicine departments can be avoided by trapping the exhaled activity on a charcoal filter. The decision to use a trap or not depends on the local circumstances. Factors that should be considered are the absolute xenon activities that are being used and the possible pathways for an eventual release out-of-doors. Individual doses from direct release of 37 GBq Xe-133 per week are negligible, except very close to the source. The collective dose depends on the density of the population in the surroundings, but is generally small. On the other hand, xenon traps are rather inexpensive devices and cost about \$ 1.000 - 2.000 (USA-funds). Usage of traps is therefore not limited by economic arguments and can in many situations be the most cost-effective solution of the ventilation problem. Reprocessing of the xenon gas also eliminates atmospheric release.

The concentration of Xe-133 in a clinical laboratory has been measured by LeBlanc and Johnson (1975) during lung ventilation studies. They found the weekly average room air concentration from 20 - 25 lung ventilation scans (0.7 GBq per study) to be 0.12 MBq/m^3 . The author of this thesis investigated the air-concentration of Xe-133 in a rCBF-laboratory at the hospital in Lund where 25 studies were performed a week (0.7 GBq per study). The mean concentration was found to be less than 0.2 MBq/m^3 per year (Bolmsjö, 1981). At this laboratory, the staff received an absorbed dose equivalent of less than 0.4 mSv per year, measured with film badges. Both investigations reported peak activity concentrations during patient investigations that could exceed $5\text{-}10 \text{ MBq/m}^3$.

Xenon gas is 4.5 times denser than air and it could be suspected that the activity stays at floor-level. In well-ventilated laboratories, the xenon gas is, however, well mixed with the room-air (Bolmsjö 1981). Spreading of

the isotope to other laboratories was measured in the Lund-investigation and it was found that only very small concentrations ($<0.5 \text{ kBq/m}^3$) could be detected outside a well-ventilated (three air-changes per hour) xenon laboratory with tightened door-steps. Outside another xenon laboratory with one cm air-gap between the door and the floor, values of between 5 - 20 kBq/m^3 were found.

These examples show that xenon isotopes can be used extensively without exceeding current recommendations of the maximum average room-air concentration or dose equivalent limits. The reported levels of airborne Xe-133 were about 1% of DAC for a room-size less than 1000 m^3 . This corresponded also very well with the low doses measured by the film badges. The spread of xenon to other rooms is minimized by properly ventilating the laboratory and using tight door-steps. Monitoring of the room-air contamination is recommendable if there exist potential risks for high levels of activity leakage, e.g. at the handling and storage of 37 GBq ampoules. Exposure from external radiation from equipment depends on the actual lead-shielding. Usage of Xe-125, Xe-127 and Xe-135 makes demands on better shielding compared to Xe-133, due to their more penetrating gamma-radiation.

The body uptake of Xe-133 in the staff due to laboratory air-contamination has been investigated in a recent study (Bolmsj , 1981). The concentration of Xe-133 in the laboratory air was continuously measured and integrated during a working day. In the afternoons, the body content of Xe-133 in the staff was measured by using a whole-body counter. Figure 4.2 shows the net count rate of Xe-133 as a function of the integrated exposure. A clear linear relationship exists. The absolute body content was not possible to calculate due to calibration difficulties, but an estimated coefficient of 10 Bq/cpm was used. The highest observed body content in Figure 4.2 then corresponded to 8.5 kBq which agrees with the expected uptake in fatty tissue according to the Ostwald coefficient.

cording to the Ostwald coefficient.

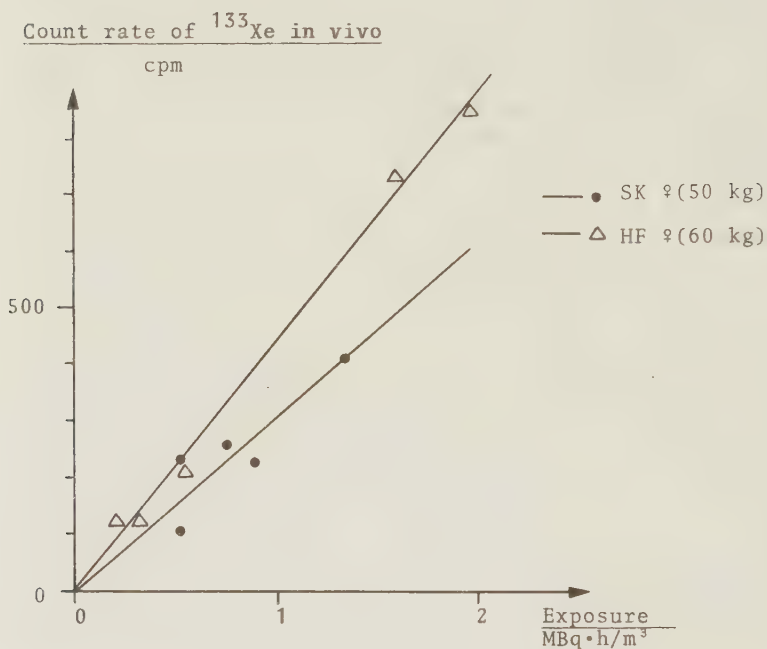


Figure 4.2: Net body content of Xe-133 in the staff of a xenon laboratory. The diagram shows the daily uptake of xenon as a function of the integrated Xe-133 concentration in the laboratory air.

5. ASPECTS OF BLOOD-FLOW MEASUREMENTS WITH XE-133

5.1 rCBF-measurements

Xe-133 is widely used for assessment of organ blood flow. At 81 keV, Compton-scattering is the dominating photon interaction process in vivo. Figure 5.1 shows the energy of Compton-scattered photons as a function of the scattering angle for a primary photon-energy of 81 keV. The energy difference between primary- and 180° backscattered photons is only 19.5 keV. Usually, NaI-scintillation detectors are used to register the washout of Xe-133 from the organ under study. The limited energy-resolution of these detectors reduces the possibility to discriminate Compton-scattered photons.

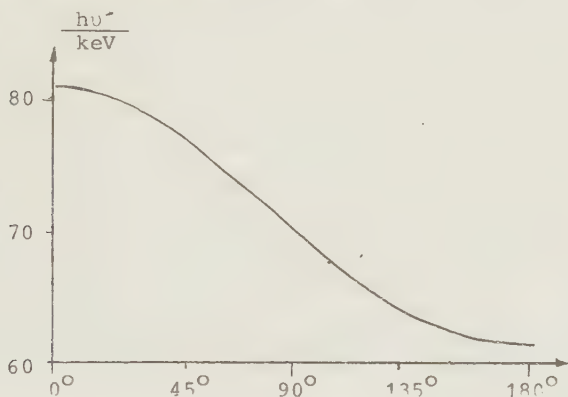


Figure 5.1: Diagram showing the energy $h\nu'$ of Compton-scattered photons as a function of the scattering angle. The energy of the primary photon $h\nu_0$ is 81 keV.

When Xe-133 is used for studies in vivo, Compton-scattering can thus contribute with signals originating outside the region-of-interest. In bilateral rCBF-measurements, hemispheric cross-talk is a further source of extra-regional influence. A study was therefore initiated with the goal of evaluating the effect of extra-regional signal contribution on the calculation of regional cerebral blood flow. See Paper IV.

Method

The three-dimensional detector response for Xe-133 in water was recorded for a NaI-detector equipped with two types of collimators. Both a broad- and a narrow- energy-window were used. A computerized simulation procedure was developed in which the experimentally determined detector-response was combined with a three-dimensional model of the brain. A region-of-interest, centrally located on one of the model-hemispheres was then simulated. It was then possible to distinguish between the signals measured from the region-of-interest to those originating from extra-regional tissues. The uptake and clearance of xenon from brain tissue, corresponding to an ordinary inhalation rCBF-study, was then simulated on the computer. Xenon-washout sequences were constructed by assuming a high or a low grey-matter flow in the region-of-interest while the remaining brain tissues were assigned normal flow values. Biexponential analyses of the simulated clearance-curves were then executed in order to calculate the grey-matter flow as measured by an external detector. The difference between actual grey-matter flow in the region-of-interest and the calculated flow derived from the analyses was then used to indicate the accuracy of regional blood flow calculations. The computer model was tested for its agreement with head-phantom measurements in order to evaluate its precision.

Results and Conclusions

The computer model was able to predict the hemispheric cross-talk as measured with the head phantom, to within 10% variance.

Of the total grey-matter signals measured by a detector located centrally over one hemisphere, only 50% were found to emanate from the grey matter in the region-of-interest. The

remaining grey-matter signals originated from the contralateral hemisphere and from parts outside the region-of-interest in the ipsilateral hemisphere. This caused artefacts in the calculation of regional grey-matter flow by 9-42% when the simulated regional flow was varied between 0.5 - 1.2 ml/min/g. Only about 50% of the simulated flow asymmetry was detected. When intra-carotid injection of Xe-133 was simulated, the maximum artefact introduced in the calculation of the regional grey-matter flow was 14%. The better resolution of regional flow differences with this administration technique is in agreement with clinical observations (Paulson, 1981).

5.2 Measurement of blood flow in rat liver.

Several techniques have been employed to calculate organ blood flow from the washout of an inert gas (Kety, 1960; Zierler, 1965). All methods generally assume a steady flow during the entire washout-period and some assume instantaneous diffusion equilibrium of xenon between the capillary blood and the tissue. If the latter assumption is valid, the transfer function of xenon-washout from the tissue is exponential (Kety, 1960). The rate of xenon-washout from the tissue is then only limited by the blood perfusion. As Kety in 1960 mentioned, the assumption of rapid equilibrium between capillary blood and tissue needs appropriate theoretical and empirical evidence to justify it. Several investigators have criticized the validity of rapid equilibrium, which, if their arguments are correct, should invalidate the derived equations (Perl, 1965; Hills, 1967; Hennessy, 1971, 1974). For rat liver tissue, Evans et al. (1974) determined the diffusion coefficient of xenon and found it to be large enough so that the washout-rate of xenon from rat liver is only perfusion-limited. For the liver, several investigators have reported two components in the washout (Darle, 1970; Sherriff et al., 1977).

The reliability and suitability of the xenon washout technique for assessment of liver blood flow on rat was investigated in Paper V. The study was initiated with the ultimate goal of finding a suitable method for blood-flow studies at experiments with hyperthermia as a new treatment method for liver cancer.

Method

Wistar rats were used for the experiments and the Xe-133 was administered by using portal vein injection, hepatic artery injection and, intraparenchymal injection. The washout-sequence of Xe-133 was registered with a CdTe-miniature detector, connected to a data-acquisition unit. The washout-curves were later analyzed on a computer by using a biexponential least square fit. The influence of different start-times and end-times of the fit on the results obtained was investigated. The fast clearance-component was used as a flow-index of the liver blood flow.

Results and Conclusions

The results showed a high degree of variance between repeated experiments on the same animal of between 18 - 27% (1 S.D.) Only larger changes in the liver blood-flow pattern during an experimental procedure can therefore be detected. The Xe-technique is, however, valuable for this purpose since repeated and regional studies on the same organ can easily be performed. Substantially faster clearance rate of the rapid component was evident when the xenon was injected directly into the liver parenchyma. This may be explained by the microcirculatory anatomy of the rat liver. The use of different start- and end-times in the mathematical least square fit was found to be a valuable tool to test the accuracy of the biexponential model.

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FACTORS AFFECTING THE TRAPPING PERFORMANCE OF XENON
HOLDUP - FILTERS IN NUCLEAR MEDICINE APPLICATIONS.

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ABSTRACT

Activated charcoal traps are used in nuclear medicine departments to capture exhaled radioactive Xenon gas. In the present study, the trapping performance of charcoal was investigated for different physical qualities in experimental and clinical situations. Various factors affecting the trapping capacity are identified, such as the charcoal mass, moisture and carbon-dioxide concentrations in the sweep gas, gas-flow rate through the trap and temperature. Improper drying of the exhaled air prior to passage through the charcoal bed appears to be a critical factor, leading to a much earlier break-through of Xenon. Commercial Xenon traps intended for ambient temperature operation were found to be useful only for a limited number of patients due to an early break-through point. By refrigerating the trap, however, a much larger capacity was achieved. If correctly managed, Xenon traps constitute a useful alternative for isolating radioactive Xenon wastes in clinical and experimental applications.

1. INTRODUCTION

Clinical investigations with radioactive Xenon tracers, such as lung function and blood-flow measurements, are well accepted and in general use in most nuclear medical centers (1,2,3,4,5). The Xenon isotope most frequently used is Xe-133. It decays to Cs-133 (stable) by beta emission with a physical half-life of 5.3 days (6). Another Xenon isotope suitable for clinical applications is Xe-127, but it is not used as often as Xe-133. It decays to I-127 by electron capture (EC, half-life=36.4d) (6).

Being an inert gas, Xenon has a short biological half-life (7). Most of the gas administered to the patient

is rapidly exchanged in the lungs and expired within a few minutes. In many centers, the exhaled Xenon waste is directly ventilated to the outdoor atmosphere. Although this method is simple, it is not always acceptable from the standpoint of radiation safety, particularly if larger amounts of Xenon are involved. At some clinics, the weekly consumption of Xe-133 is 37 GBq (1 Ci) or more. Atmospheric release of such a large activity must be carried out so that there is no risk of the gas re-entering the building through open windows or room-ventilation intakes (8). An alternative method is to use a Xenon trap which captures the radioactive waste. The exhalation air from the patient is then pumped through a filter which separates and traps the Xenon gas.

Methods for trapping Xenon have been developed for nuclear power installations, such as adsorption on activated charcoal, cryogenic condensation, absorption in fluorocarbon and permselective membranes (9,10). For small-scale filter application, e.g. for nuclear medical purposes, adsorption in activated charcoal appears to be the most economical technique (11,12,13,14,15). In the adsorption process, the Xenon atoms are weakly bound to the charcoal due to unbalanced forces on the charcoal surface (16). The binding is generally weak (Van der Waal forces), and hence the adsorption of a Xenon atom is eventually followed by desorption, i.e. the Xenon atom is freed. Air flow carries the desorbed Xenon atoms forwards in the trap. New adsorption events occur frequently, however, thereby reducing the speed of the Xenon's progress through the trap. Finally, break-through of the activity occurs at the effluent side of the trap. To minimize the discharge of radioactive Xenon, trap design should preferably optimize the relation between the time the Xenon is adsorbed and its physical decay.

Among the physical factors determining the duration of the Xenon-holdup in the trap are the charcoal mass, its

quality, the trap geometry, the air-flow rate through the trap and the operating temperature (17,18,19,20). Carbon dioxide and moisture have previously been observed to reduce the adsorption capacity for Krypton and Radon (17,21). Expired air contains considerable amounts of these two components, which indicates that gas-drying procedures may be necessary for clinical usage of activated charcoal traps. To obtain a practical management of Xenon traps, they should have a capacity large enough for rather many patient investigations.

The performance and limiting factors of charcoal-based traps have been studied in the present investigation. Model traps as well as commercially available Xenon traps were tested, in both laboratory and clinical situations. The results of these experiments lead to the construction of an improved, refrigerated trap, that is effective for long periods of time with a large number of patients.

2. MATERIALS and METHODS

2.1 The theoretical model

The experimental set-up used for investigating the dynamic behaviour of activated charcoal in Xenon adsorption is shown in Figure 1. A short pulse of Xe-133 was injected at the bottom of a charcoal column while the air pump continuously forced an even air flow through the trap. As the Xenon moved forward in the trap, it finally became detectable in the output gas at the top and was measured with an ionization chamber (Triton 1055B, Johnston Laboratories, Inc., USA).

The mathematical model used for interpreting the effluent trap activity was that proposed by Browning and Bolta (22). The model assumes that the charcoal column consists of a finite number of compartments or chambers connected in a series. Xenon introduced into a chamber is assumed to be instantly and homogeneously distributed throughout the entire chamber.

Introducing the quantities $P_i(t)$, $Q_i(t)$ and $R_i(t)$, where $P_i(t)$ is the Xenon activity in chamber i , $Q_i(t)$ is the rate of activity input into the chamber and $R_i(t)$ is the rate of activity output, the time derivative of Xenon present in chamber i is:

$$\frac{dP_i(t)}{dt} = -R_i(t) + Q_i(t) \quad (1)$$

By using the compartment concept, the fractional rate of activity output from a chamber is determined by the rate of gas flow through it, divided by the virtual gas volume in the chamber. The output rate from chamber i is thus:

$$R_i(t) = \frac{F \cdot N}{k \cdot m} \cdot P_i(t) \quad (2)$$

where N is the number of chambers in the trap and m is the total charcoal mass (gram). The quantity F is the rate of gas flow through the trap (l/min). The coefficient k (l/g) is the dynamic adsorption coefficient, which, multiplied by the mass of charcoal in a chamber (m/N), reflects the virtual gas volume of the chamber. This parameter reflects the role of charcoal in the adsorption process. Since the chambers are connected in a series, the input rate to chamber $i+1$, Q_{i+1} , equals the output rate from chamber i , R_i .

Assuming an instantaneous injection of Xenon into the first chamber at zero-time, the concentration of Xenon in the output from the last chamber can be derived as (see Appendix for derivation of all the equations given below):

$$C_N(t) = B \cdot \left(\frac{N}{k \cdot m}\right)^N \cdot \frac{(F \cdot t)^{N-1}}{(N-1)!} \cdot \exp\left(-\frac{F \cdot N \cdot t}{k \cdot m}\right) \quad (3)$$

where $C_N(t)$ is the activity concentration in the effluent gas stream, B is the input activity into the trap at zero-time and t is the elapsed time.

The time $t_{\max}$ after start, when the Xenon concentration in the effluent gas is at its maximum, relates to the dynamic adsorption capacity k , by

$$t_{\max} = \frac{(N-1) \cdot k \cdot m}{N \cdot F} \quad (4)$$

The number of theoretical chambers in the trap, N , is given by

$$N = \frac{\ln(A(t))}{\ln(t/t_{\max}) + 1 - (t/t_{\max})} + 1 \quad (5)$$

where

$$A(t) = \frac{C(t)}{C(t_{\max})} \quad (6)$$

i.e., $A(t)$ is the discharge of radioactivity at time t relative to the discharge at time $t_{\max}$. As indicated by equation 4, a high value of k is favourable in order to maximize the trapping capacity. The shape of the output-activity profile is dictated by N . A large value for N implies a delayed Xenon break-through and is thus preferable to a smaller value for N .

The parameter of direct interest for the physician and the radiation physicist is the break-through point V_b , which reflects the accumulated air-volume passage at which the trap begins to discharge substantial amounts of Xenon and eventually should be replaced. For the traps investigated in this study, the following approximative formula corresponded well with experimental data:

$$V_b \approx k \cdot m \cdot (1 - \sqrt{-\ln(A(t_b)/(N \cdot I))}) \quad (7)$$

In this study, $A(t_b)$ at the break-through point V_b was chosen as 0.02, selected to ensure a very low release of activity prior to that point.

2.2 Experiments.

Model Traps.

Two smaller traps were used to investigate the adsorption characteristics for Xenon under different physical conditions. The traps were made of $\varnothing$ 37 mm brass tubes, 1.0 and 0.94 m in length, respectively. Charcoal of coconut shell was used, Picatif G210 (Pica, France), with a specific surface area of 1100 - 1200 m²/g. This charcoal has data comparative with other types available for Xenon adsorption (19,20). Different deliveries of the charcoal from the same factory were used in the two traps. The charcoal was care-

fully packed in the traps so as to have no void spaces (17). The charcoal masses in the traps were 462 g and 431 g, respectively. Before the traps were taken into use, they were regenerated for 1 hour at 300°C during evacuation (approximately 95% vacuum).

For each measurement, a short pulse of Xe-133, 3.7 - 37.0 MBq (0.1 - 1.0 mCi) was injected at the bottom of the trap as shown in Figure 1. Pure air was used as sweep gas. From the output-gas activity recordings, the model parameters k and N were determined by using equations 4&5. To determine N , a least-square fit of equation 5 was applied. The fit was limited to values of $A(t)$ ranging between 0.2 and 0.8, since equation 5 is sensitive to fluctuations in the data when $A(t)$ is close to 0 or 1. The break-through point V_b was obtained directly from the trap effluent recordings.

The measurements were carried out to study the effects of:

- a) different rates of sweep-gas flow through the trap,
- b) deterioration of the charcoal due to long usage,
- c) moisture and
- d) carbon-dioxide in the sweep gas.

The gas flow through the trap was varied from 1.5 l/min to 17 l/min. Deterioration effects due to large air volume passage, 125 m^3 , were examined. The moisture content in the sweep gas was alternated between 3 and 6 grams of water per m^3 , respectively, representing well- and moderately well dried air. Measurements were also performed with humid sweep gas; 18 grams of water per m^3 . Finally, 5% carbon-dioxide was added to the sweep gas in order to simulate exhalation air.

The theoretical model does not account for pure diffusion of trapped Xenon. Its magnitude was therefore investigated by injecting a Xenon bolus at the centre of the 431 g trap and recording the dispersion of the activity during the

subsequent two days without gas flow through the trap. The propagation of a Xenon pulse with gas flow present ($F=10$ l/min) was also recorded in order to convey an accurate impression of the trapping mechanism. These activity profiles were obtained by scanning the trap with a collimated NaI-scintillation detector connected to a multichannel analyzer using the multiscaling mode (Nuclear Data ND100, USA).

The temperature during the above described experiments was kept constant at $21 \pm 1^\circ\text{C}$.

Clinical Traps

The trapping performance of two commercial charcoal traps, "MXT 1" from Novo Diagnostic Systems, Denmark, and "NONEX" from Nuclear Associates, USA, was studied. "MXT 1" contained 7 kg of the charcoal type "Picatif G210" and "NONEX" 5 kg of a similar type, "617" from North American Carbon, USA. (23,24). They differed only slightly in constructional details. Both the traps consisted of smaller segments connected in a series. The traps were intended to operate at room temperature, so that the temperature was kept at 20°C . The traps were studied both in laboratory tests, with Xe-133 injected as a pulse according to Figure 1, and in nuclear medical patient investigations. The rates of sweep-gas flow in the laboratory tests were 5 and 15 l/min and the gas humidity was 6 g/m^3 . Deterioration of the traps due to large volumes of air passage (500 m^3), was again examined, as well as effects of carbon-dioxide present in the sweep gas.

The clinical tests of the traps were performed in connection with regional blood-flow measurements, rCBF. Xe-133 was inhaled for 1 minute (approximately 80 MBq/l) followed by 10 minutes washout with the patient connected to the trap. The total activity exhaled and trapped during an investigation was approximately 370 MBq (10 mCi). The number

of patients varied from 0 to 11 per day with a mean of 5. The traps were set up with the air pump running in short on- and off-periods in order to follow the actual exhalation rate (see Figure 2). During on-periods, the air flow was 10 liters per minute. The exhaled gas was dried in a silica gel-filter before being pumped through the trap.

Refrigerated trap

Refrigeration of charcoal traps greatly increases the trapping capacity. This is due to a strong relation between the dynamic adsorption capacity, k , and the reciprocal temperature, $k \sim \exp(1/T)$, where T is in Kelvin (17,18,19,20).

A refrigerated system was designed with a charcoal trap containing 6.5 kg of Picatiff G210, installed in a freezer (Philips, type AAB 800). The same set-up as shown in Figure 2 was adopted. The silica gel-filter was, however, replaced by a small container inside the freezer. Moisture in the exhaled gas was frozen to ice in this container before being pumped through the trap. The temperature of the charcoal cartridge was kept below -20°C . The refrigerated trap was tested in the same manner as the two commercial traps.

3. RESULTS

3.1 Model Traps

Even if the physical principles of Browning's Theoretical Chamber Model can be questioned, it has the advantage of being rather simple and to correspond well with experimental data. A typical experimental effluent-activity profile is shown in Figure 3. The activity was injected as a bolus on the inlet side of the trap and air was continuously pumped through it at the rate of 10.9 l/min. In the situation depicted, Xenon break-through occurred after 180 liters of gas passage and the maximum discharge of activity took place after the passage of 370 liters. The open circles in the diagram represent experimental recordings, while the straight line indicates the theoretical prediction. The strong correlation between the experiments and the theoretical model is clearly demonstrated.

To illustrate the trapping mechanism, the dispersion and propagation of a Xenon bolus in the 431 g trap are shown in Figure 4a. The activity distribution in the trap is shown after different sweep-gas passage, 10, 160 and 350 liters, respectively. After 10 liters of gas flow, all activity is still adsorbed in the trap, although the forward movement is obvious. The situation at or near the break-through point is reflected after 160 liters of sweep gas. The activity centre has moved substantially and small amounts of Xenon are released in the output gas. After 350 liters of gas flow, most of the activity has escaped from the trap.

The magnitude of pure diffusion in the trap is indicated in Figure 4b. It shows the dispersion of a Xenon bolus without sweep gas at 0, 24 and 48 hours after injection of the activity. As can be seen, the diffusion rate is low.

The effects of different rates of sweep-gas flow through the

traps on the model parameters k , N and V_b are shown in Figure 5(a,b,c). Each point in the figures represents the mean value of 1 - 3 runs. According to Figure 5a, the adsorption capacity, k , is not significantly affected by different flow rates, while the number of chambers, N (Figure 5b), shows a strong dependence. Consequently (cf Eq.7), the break-through point V_b is dependent on the flow rate, which is also verified in Figure 5c. In order to detect eventual deterioration of the charcoal, Figure 5 shows the data obtained during the first 10 m³ of sweep-gas flow after regeneration (sweep-gas humidity was 3 g/m³), separated from the data obtained during 10 - 125 m³ of gas flow (sweep-gas humidity was 6 g/m³). Although the charcoal mass increased a few percent during the latter series - probably due to absorption of water, no major differences in the trapping performance of the two groups were observed. Large volumes of sweep gas do not thus seem to be a limiting factor for charcoal-based Xenon traps. A minor difference (6%) in k was found between the 431 g and the 462 g traps, possibly caused by small variations in the manufacturing process used to produce the charcoal. The results between the two traps are very similar.

The effects of water uptake in the trap were measured by using humid air (18 g/m³) as sweep gas. About 8 grams of water was accumulated in the trap per m³ of gas flow. The water reduced the model parameters substantially (see Figure 6(a,b,c)). Compared with the dry trap, a water uptake of 190 g reduced the break-through point from 180 liters to only 1.5 liters.

The addition of 5% carbon-dioxide to the sweep gas resulted in a 20% reduction of k and a 30% reduction of V_b (see Table 1). A total of 5 m³ CO₂-traced sweep gas was blown through the 462 g trap. The effects on the model parameters were constant during the entire experiment, indicating that CO₂-saturation was quickly achieved. When normal air was

again used as sweep gas, the parameters returned to their previous values.

3.2 Clinical Traps

The results from the laboratory studies of the "MXT-1" and the "NONEX" traps are summarized in Table 2. The dynamic adsorption capacity, k , was of the same order as for the model traps. This was also expected from the theoretical model. The number of theoretical chambers, N , appears to be a more complex parameter. The expected decrease of N at the higher flow rate (15 l/min), was only observed for the "NONEX" trap. The "MXT-1" trap, however, showed an eventual increase in N at the higher gas-flow rate, although it was not statistically significant. This could be a geometrical effect: the "NONEX" trap was cylindrical, but the "MXT-1" consisted of square tubes. Flow asymmetries may then occur, especially at the corners. The break-through of Xenon occurred at between 2.1 and 3.3 m³ with a slight advantage for the "MXT-1". This is obviously due to the different charcoal masses in the two units. Exposing the traps to CO₂-admixture sweep gas reduced the break-through point by 25% for the "MXT-1" trap and by 30% for the "NONEX" trap. More than 500 m³ of sweep gas with a humidity of 6 g/m³ was blown through the two units without any serious reduction of the trapping effectivity. The total life-time of the charcoal thus seems to be very high.

Table 2 indicates the length of running time for the traps before they should be replaced. It must, however, be borne in mind that the clinical situation differs from the laboratory environment. In the first place, the presence of carbon-dioxide in the exhalation air automatically reduces the trapping capacity by 25 - 30%. Secondly, Xenon is not supplied as a single bolus, but more or less continuously. Thirdly, a small number of patient investigations will allow

a substantial decay of the trapped Xenon, which increases the running time. In the fourth place, although diffusion of trapped Xenon is a slow process, it may have some influence on the length of the running time, since a trap is normally used several weeks or months.

The performance of the traps in clinical use is shown in Figure 7(a,b), presented as the output activity³ versus the accumulated air-flow passage. On an average, 2 m³ of exhalation air (20 patients) could be blown through the traps before the output-gas activity reached the MPC-level for Xe-133, 0.37 MBq/m³ or 10 uCi/m³. This level corresponds to 0.1 DAC of the new "Derived Air Concentration" concept, proposed by ICRP (25,26). The absolute output-gas discharge at the 1 MPC-level is, however, only 37 kBq (1 uCi) per patient, when 100 liters of air is collected per investigation. Compared to the input activity per patient, 0.37 GBq (10 mCi), a very low activity, was thus discharged at this point. When the dilution in the air in the room is taken into consideration, it appears that a discharge of up to 1-2 MBq (25 - 50 uCi) during short intervals, could hardly result in excessive radiation doses for the staff. Depending on the ventilation facilities of the department, the practical running time of a trap can thus exceed the 1 MPC discharge point.

The negative effect of not drying the exhaled air before pumping it through the trap was seen for both the traps. If this is done repeatedly, the capacity of the trap will be greatly reduced.

Refrigerated Trap

The results of the experiments with the refrigerated trap are given in Table 2. Compared to the "MXT-1" or the "NONEX" traps, the increase in capacity is clearly seen. In

a first study, air was sucked through the trap instead of being blown through it. This arrangement was, however, abandoned since immediate break-through of activity occurred, probably caused by excessive channeling in the trap. This effect was never observed when the pump was installed as shown in Figure 2.

The trap performance in the clinical situation is shown in Figure 7c. Only a very low release of activity was observed during the entire test period (150 patients). The practical running time thus seems to exceed 15 m^3 of air passage. The refrigerated trap thus appears to be superior to the others from practical points of view. Xenon remains in the trap long enough to allow for substantial physical decay of the trapped Xe-133, also during periods with frequent patient investigations.

DISCUSSION

The results of the study show that activated charcoal traps are effective for clinical purposes. Exhalation air must, however, be dried before being transported to the charcoal. A humidity content of up to 6 g/m^3 in the sweep gas did not affect the trapping performance and a simple drying procedure is thus sufficient, e.g. with silica gel. Presence of carbon-dioxide in the sweep gas did not reduce the trapping capacity as heavily as water did. Carbon-dioxide drying agents do not thus appear to be mandatory. If used, they should be properly chosen. At least one CO_2 -absorber (soda lime) forms water when reacting with water and hence creates a new problem while solving another one. If the trap should become damp, it can be dried by heating it to 80°C and blowing dry air through it for a couple of hours. The model traps were completely dried in less than 2 hours by using this technique. The model parameters then returned to their normal values.

The break-through point is somewhat increased by using a low rate of sweep-gas flow. This is, however, in conflict with other practical considerations, since the patient's exhalation rate is rather high, around 10 l/min. Several commercial traps use a low rate of gas flow, e.g. 5 l/min for original "NONEX" traps, and therefore need an extra expandable interface bag to be connected between the patient and the trap. Other traps run faster, e.g. 15 l/min for original "MXT-1" traps, and should normally not require this interface. The pulse mode operations of the air pump used in this study were found to be practical since the trap started to work automatically as soon as it was connected to the patient.

It is of course desirable to get some indication of the activity discharged from the trap. Continuous monitoring of

the effluent gas should, therefore, be beneficial. Several reports exist concerning measurement techniques for Xenon levels around 1 MPC (27,28,29).

Charcoal cartridges that have been removed from the trap may be stored until they reach a low level of activity by natural decay. Normally, the cartridge should then be ready for re-use. Blowing dry heated air through the trap before taking it into use again may eventually be of benefit.

Manufacturers of commercially available Xenon traps do not always specify the capacity of their products. A diagram like Figure 3 or Figure 7 should be of great help for the user. For high Xenon-consumers, as was the case in this study, a running time of 2 - 4 m³ is too low to be acceptable. By using refrigerated traps, a great increase in capacity is achieved, which minimizes cartridge-exchange procedures. A few refrigerated traps have recently been introduced on the market.

If the trap is intended for Xe-127, Figure 7 is not valid because of the long half-life of that isotope. The amount of Xe-127 used in clinics is, however, generally much less than that of Xe-133. Furthermore, re-cycling of Xe-127 may be beneficial, as it brings the isotope into a closed loop system (20).

APPENDIX

Equation 1 in the text (eq.A1 below) describes the mass balance of Xenon adsorbate in chamber i. Using the one-compartment concept, the output rate of Xenon from a chamber is described by eq.A2.

$$\frac{dP_i(t)}{dt} = -R_i(t) + Q_i(t) \quad (A1)$$

$$R_i(t) = \frac{F \cdot N}{k \cdot m} \cdot P_i(t) \quad (A2)$$

Assuming a delta function input of Xenon into chamber 1 with a strength B, eq.A1 is reduced to

$$\frac{dP_1(t)}{dt} = -\frac{F \cdot N}{k \cdot m} \cdot P_1(t), \quad P_1(0) = B \quad (A3)$$

which, if solved yields

$$P_1(t) = B \cdot e^{-\frac{F \cdot N \cdot t}{k \cdot m}} \quad (A4)$$

This equation describes the washout of Xenon from a chamber following a bolus injection of the activity and thus characterizes the transfer function of a single chamber. Since a serial system is assumed, the activity discharged from chamber 1 enters chambers 2. From eq.A2 it follows that the input activity rate into chamber 2 is:

$$Q_2(t) = \frac{F \cdot N}{k \cdot m} \cdot B \cdot e^{-\frac{F \cdot N \cdot t}{k \cdot m}} \quad (A5)$$

By convoluting eq.A5 with the exponential transfer function (cf. Eq.A4), the Xenon present in chamber 2 at any time t is achieved:

$$P_2(t) = \int_0^t Q_2(\tau) \cdot e^{-\frac{F \cdot N}{k \cdot m}(t-\tau)} d\tau = B \cdot \frac{F \cdot N \cdot t}{k \cdot m} \cdot e^{-\frac{F \cdot N \cdot t}{k \cdot m}} \quad (A6)$$

This procedure is valid if the adsorption of Xenon is strictly linear, i.e. the amount of Xenon being adsorbed is a linear function of the partial pressure of the gas. This assumption is justified for the low concentrations of Xenon that are used in nuclear medicine (17,19).

The input rate to chamber 3 is then formed by:

$$Q_3(t) = \frac{F \cdot N}{k \cdot m} \cdot P_2(t) \quad (A7)$$

etc.

The general analytical expression, giving the amount of Xenon present in the last chamber ($i=N$) is obtained as:

$$P_N(t) = \frac{B}{(N-1)!} \cdot \left\{ \frac{F \cdot N \cdot t}{k \cdot m} \right\}^{N-1} \cdot e^{-\frac{F \cdot N \cdot t}{k \cdot m}} \quad (A8)$$

The output rate from the trap is then obtained as:

$$R_N(t) = \frac{F \cdot N}{k \cdot m} \cdot P_N(t) \quad (A9)$$

Hence, the concentration in the outlet is found to be:

$$C_N(t) = \frac{R_N(t)}{F} = B \cdot \left\{ \frac{N}{k \cdot m} \right\}^N \frac{(F \cdot t)^{N-1}}{(N-1)!} \cdot e^{-\frac{F \cdot N \cdot t}{k \cdot m}} \quad (A10)$$

which is eq.3 in the text.

By time derivate eq.A10 and setting the result to zero, the time, $t_{\max}$, when the output gas concentration of Xenon is at its maximum, is

$$t_{\max} = \frac{(N-1) \cdot k \cdot m}{N \cdot F} \quad (A11)$$

which is eq.4 in the text.

The output gas concentration at time t , $C(t)$, relates to the concentration at time $t_{\max}$, $C(t_{\max})$, as:

$$A(t) = \frac{C(t)}{C(t_{\max})} = \left[\frac{t}{t_{\max}} \right]^{N-1} \cdot \frac{e^{-\frac{F \cdot N \cdot t}{k \cdot m}}}{e^{-\frac{F \cdot N \cdot t_{\max}}{k \cdot m}}} \quad (A12)$$

which, combined with eq. A11 yields:

$$N = \frac{\ln(A(t))}{\ln(t/t_{\max}) + 1 - (t/t_{\max})} + 1 \quad (A13)$$

i.e, equation 5 in the text.

By dividing equation A11 with the time at the break-through point, t_b , and recognizing that $V_b = t_b \cdot F$, an approximative equation for V_b is:

$$V_b = \frac{t_b \cdot k \cdot m}{t_{\max}} \quad (A14)$$

The ratio $t_b/t_{\max}$ can be obtained from eq.A13. For the traps studied, the ratio was greater than 0.5 and a reasonably accurate approximation of the $\ln(t_b/t_{\max})$ -term is the first two terms in the Maclaurin expansion of $\ln(1+x)$.

when this approximation is used, the break-through point V_b can be simplified to:

$$V_b \approx k \cdot m \cdot (1 - \sqrt{-\ln(A(t_b)) / (N-1)}) \quad (A15)$$

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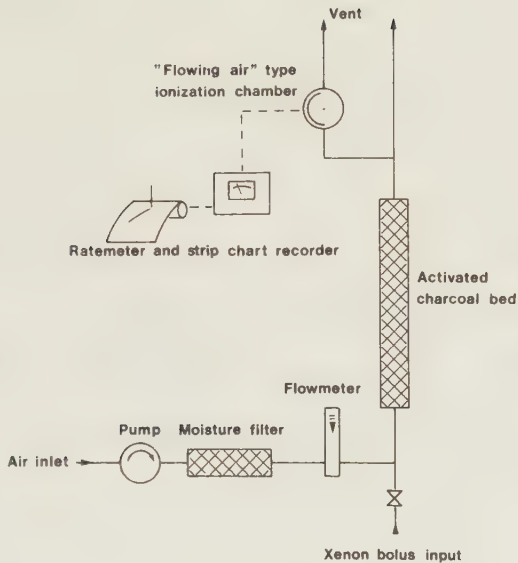


Fig.1. Experimental set-up for measurement of the dynamic trapping characteristics for Xe-133.

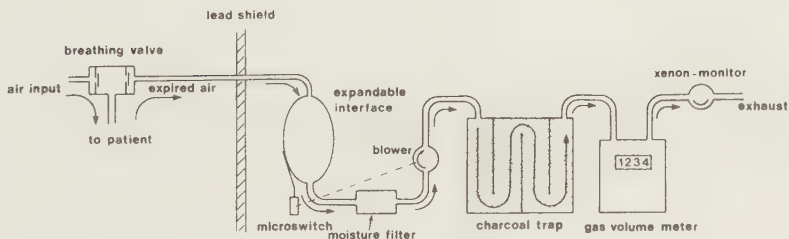


Fig.2. Set-up for the clinical trap tests. The patient exhales into the expandable interface (a plastic balloon with 25 l maximum capacity). During interface expansion, the spring-loaded microswitch activates, thus turning the blower on. The exhaled gas is then in turn passed through the silica gel-filter and the charcoal trap. The total accumulated air-volume passage through the trap is measured by the gas-volume meter. The output activity is measured by an ionization chamber.

Relative activity release

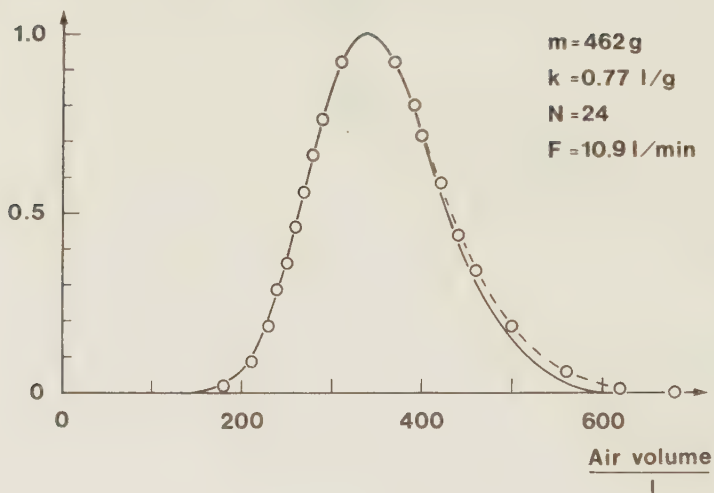


Fig.3. Recording (open circles) of the Xe-133 release from the 462 g model trap following a pulse-input injection. The abscissa is the accumulated air volume passed through the trap, counted from the moment of injection. The drawn line is the fit for equation 5 to the experimental data.

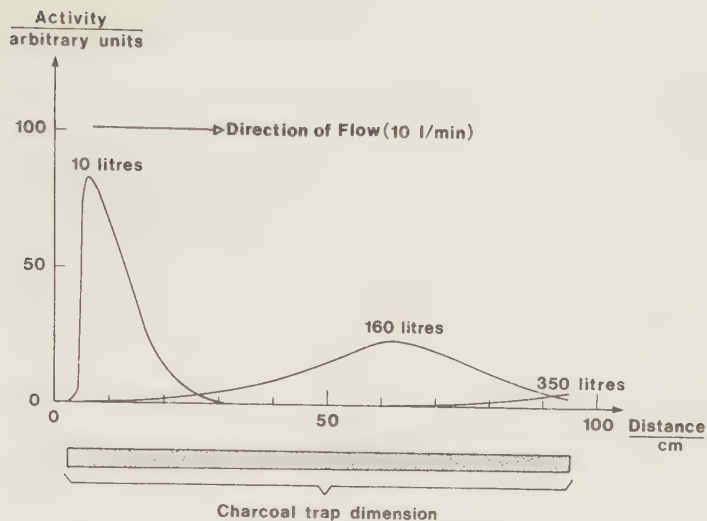


Fig.4a. Illustration showing the trapping of a Xenon pulse (431 g trap) and the subsequent forward move due to the air flow ($F=10$ l/min). The activity profiles correspond to a total air-volume passage of 10 l, 160 l and 350 l, respectively, counted from the moment of injection.

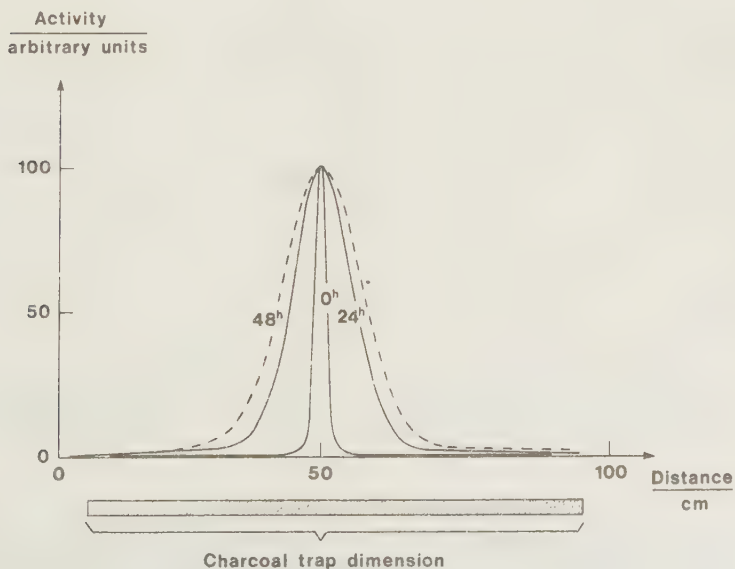


Fig.4b. Illustration of the diffusion of an adsorbed Xe-133 point source, administered at the center of the trap (431 g) at time 0. The activity profiles correspond to 0 h, 24 h and 48 h, respectively, after the administration of the isotope.

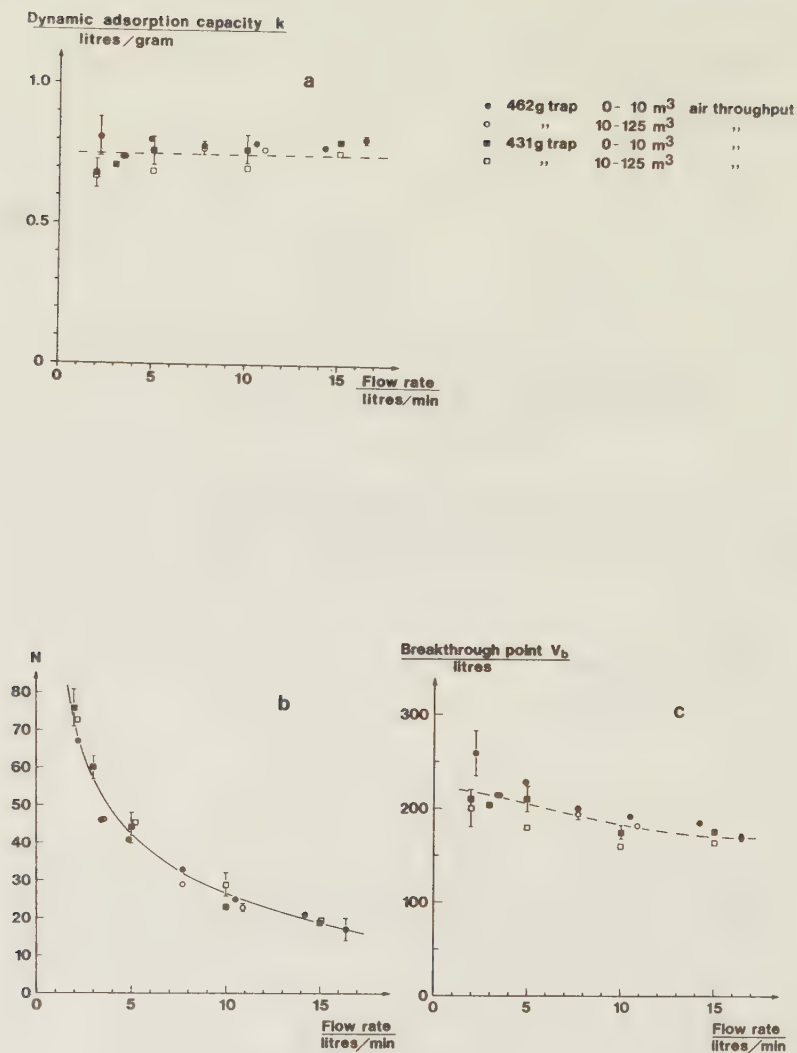


Fig.5. The trap parameters k , N and V_b for the 431 g and the 462 g traps at different flow rates and air-volume passage. Typical uncertainties in the data are shown, derived as the combination of the data spread between different runs and systematic uncertainty.

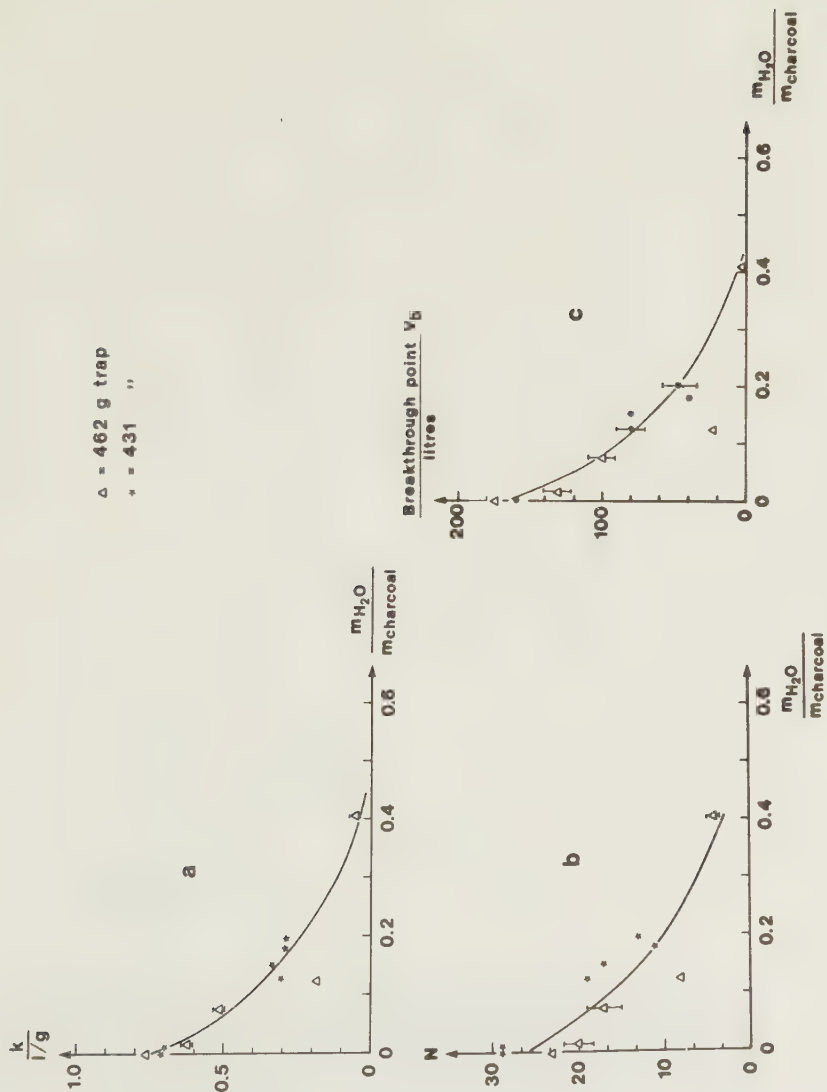


Fig.6. The trap parameters k , N and V_b for different amounts of water absorbed in the 431 g and the 462 g traps. The gas-flow rate was 10 l/min. The abscissa is the ratio of the water mass absorbed to the dry charcoal mass.

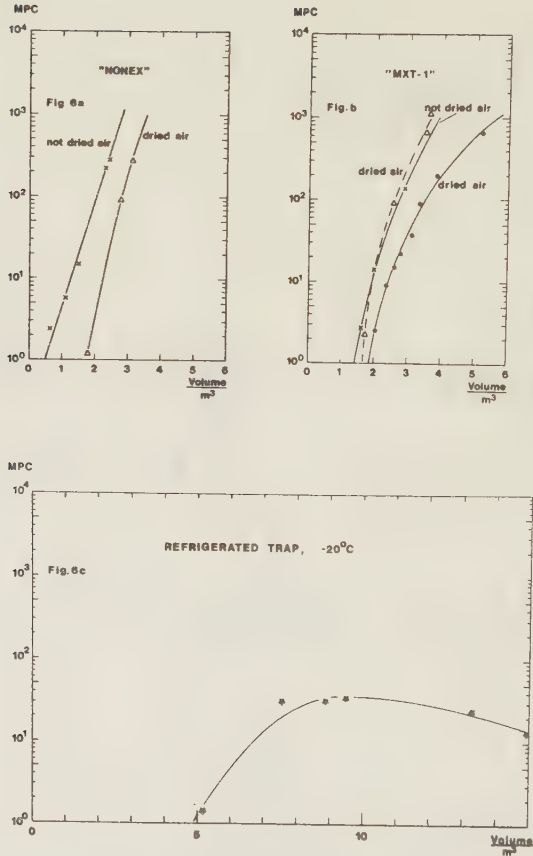


Fig.7. The Xe-133 activity concentration in the output gas at the clinical tests of the NONEX-trap (Fig.7a), the MXT-1 trap (Fig.7b) and the refrigerated trap (Fig.7c). Data is presented as a function of the total air passage counted from the first patient. The mean expired air volume passed through the traps was 100 liters per patient. The mean patient frequency was 5 studies per day, 5 days a week. Figs.7a and 7b also show the effect on the trapping capacity of not drying the exhaled air before pumping it through the trap. The Δ -curve in Fig.7b was obtained after the "not dried" run without any drying procedure of the trap in between. The mean input concentration of Xe-133 to the traps was 10,000 MPC.

Charcoal Mass (g)	Sweep Gas	Flow rate (l/min)	k (l/g)	N	V_b (l)	No of runs
462	CO ₂ -free air (6g H ₂ O per m ³)	10.9 $\pm$ 0.2	0.77 $\pm$ 0.01	23 $\pm$ 1	183 $\pm$ 4	3
462	5% CO ₂ added to dry air (3g H ₂ O per m ³)	10.9 $\pm$ 0.2	0.64 $\pm$ 0.01	23 $\pm$ 8	137 $\pm$ 5	3

TABLE 1. The effect of carbon-dioxide in the sweep gas on the trap-specific parameters k , N and V_b . The table also shows the trap parameters for carbon-dioxide-free sweep gas for comparative purposes.

Charcoal Mass (g)	Temperature ($^{\circ}\text{C}$)	Flow (l/min)	k (l/g)	N	V_p (l)	No of runs
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"NONEX"

5000	20	5.0 $\pm$ 0.2	0.80 $\pm$ 0.03	45 $\pm$ 11	2700 $\pm$ 100	2
5000	20	15.0 $\pm$ 0.2	0.75 $\pm$ 0.02	24 $\pm$ 6	2125 $\pm$ 40	3

"MXT-1"

7000	20	5.0 $\pm$ 0.2	0.71 $\pm$ 0.03	30 $\pm$ 7	3025 $\pm$ 120	2
7000	20	15.0 $\pm$ 0.2	0.73 $\pm$ 0.02	38 $\pm$ 10	3325 $\pm$ 125	4

Refrigerated Trap

6500	-22	20.0 $\pm$ 0.5	2.74 $\pm$ 0.2	27 $\pm$ 5	$\bar{x}$	1
6500	-19	15.0 $\pm$ 0.5	2.46 $\pm$ 0.1	18 $\pm$ 1	7300 $\pm$ 300	1

TABLE 2. Table of the experimental trap parameters k , N and V_p for the "NONEX", the "MXT-1" and the refrigerated trap. The humidity in the sweep air was constant at 6 g/m³ during the tests, except for the refrigerated trap, where it was less than 1 g/m³. * In the first study of the refrigerated trap, the pump drew air through the trap instead of blowing it. It was observed that some Xenon appeared immediately in the output gas with this pump arrangement, while the major part of the activity followed the expected hold-up distribution. This effect is believed to be caused by channeling in the charcoal. This pump arrangement was therefore abandoned.

Trapping and Re-use System for Radioactive Xenon in Nuclear Medicine

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ABSTRACT. Different methods of trapping radioactive xenon are reviewed. Trapping by adsorption on activated charcoal has the advantage of being simple and cheap and also makes it possible to recycle the xenon. An activated charcoal trapping system is described which can extract ^{133}Xe from 100 l of expired air in 10 min from patients undergoing diagnostic pulmonary or circulation studies. Details of the construction are discussed. The trapped gas can be rapidly released and returned to the spirometer. Substantial reduction of costs can be achieved with ^{133}Xe ; this becomes even more important as accelerator-produced ^{137}Xe comes into more general use.

1. Introduction

The usefulness of radioactive xenon for medical diagnostic purposes is well documented and examples of common applications are functional pulmonary studies and blood flow measurements. Because of the relatively high cost of radioactive xenon, it would be economical to employ a system that enables re-use of the xenon gas. In most applications the xenon gas is inhaled from a spirometer and the need for highly concentrated xenon does not therefore occur. Almost all the activity absorbed in the body will be expired within five to ten minutes after the inhalation of xenon has ended. By collecting the expired air, which would probably not exceed 100 litres and pumping it through a trap, the xenon can be removed from the air stream if a proper trap is designed.

Various techniques are known for trapping radioactive noble gases, developed as a result of the increasing number of nuclear power reactors and fuel recovery plants. Since these gases are produced in large quantities in the fission process (the fission yield of ^{133}Xe is about 7% in ^{235}U -fission), trapping systems have been constructed to retain most radioactive noble gases for a period of several half-lives (Keilholtz 1971). An example of such a system in the medical field is the so called 'life time xenon trap'.

The most usual techniques for gas hold-up systems in the nuclear power industry involve one or more of the following processes: adsorption by charcoal at room temperature, refrigerated charcoal adsorption, cryogenic distillation, solution in fluorocarbon and separation by permselective membranes. Each process has its own particular merits and limitations as summarised below.

Adsorption of noble gases on charcoal can be explained as a series of progressive adsorption-desorption steps that slow down the adsorbate velocity relative to the carrier gas stream. In conventional operation the process gas stream passes through the charcoal bed until a 'breakthrough' occurs; i.e. until the concentration of radioactivity in the effluent gas reaches a specified level. The time the charcoal will retain the adsorbate increases with decreasing temperature. The principal benefit obtained with refrigerated charcoal beds, which are often designed for operation near the temperature of liquid nitrogen, is thus a small trap size.

In cryogenic systems the noble gases and part of the carrier gas are first liquefied. The noble gases are then separated by fractional distillation. In all low temperature operations condensable gases like water vapour and carbon dioxide must be removed before refrigeration of the gas stream, otherwise ice and other solids may give rise to acute problems. There is also an explosion hazard with refrigerated systems due to accumulation of explosive materials such as liquid ozone, which is formed from the radiolysis of oxygen. One also has to consider the danger from pressure build-up if refrigeration is lost.

In the fourth process mentioned, the gas stream is extracted with liquefied fluorocarbon. Xenon and krypton are more soluble than argon, oxygen or nitrogen and are therefore removed from the gas stream as it bubbles through the fluorocarbon.

The permselective membranes technique utilises the differential permeability of the gas stream components, especially for noble gases compared to oxygen and nitrogen (Browning 1960, Keilholtz 1971).

Each of these processes can be used for efficient removal of radioactive xenon. However, in constructing xenon traps suitable for medical purposes one must consider this application as a very small scale plant compared to the requirements in the nuclear industry. Adsorption of xenon on charcoal at or near room temperature for this purpose is undoubtedly the simplest and cheapest method. All the other techniques have the disadvantage of complex and expensive equipment.

Trapping of xenon for medical purposes has been discussed in a number of recent papers. A cryogenic system has been described by Mantel, Cook and Corrigan (1968) and Corrigan Mantel and Corrigan (1970), using liquefied nitrogen as the coolant. The use of activated charcoal for containment of ^{133}Xe was discussed by Liuzzi, Keaney and Freedman (1972) and Timpe (1976) and the former also noted the possibility of recycling the trapped xenon.

Vaalburg, Peset, Beekhuis, Woldring and Tammeling (1971) have briefly described a recovery system for lung function studies using 100 g of activated charcoal chilled to -80°C . A refrigerated system was also described by Forouzan-Rad (1976) who used steam for releasing the trapped xenon.

In the system described in the present work the trapping is done at room temperature and the release of the trapped xenon is achieved by heating the trap to a temperature at which the xenon is no longer bound to the charcoal; the gas is rapidly recollected in the spirometer by blowing a sweep gas through the bed.

2. Materials and methods

2.1. The adsorption process

Physical adsorption of a gas (the adsorbate) on a solid (the adsorbent) can be regarded as a condensation of the gas on the surface of the adsorbent. Thus, adsorption is an exothermic reaction. The process of adsorption exhibits the following characteristics:

(a) The amount of gas adsorbed per unit mass of adsorbent increases as the partial pressure of the gas is raised. Various empirical and theoretical equations have been suggested to express this behaviour; one of the best known is the Freundlich Isotherm equation:

$$A = kP^{1/n} \quad (1)$$

where A represents the equilibrium amount of adsorbed gas per unit mass of adsorbent at a constant temperature, P represent the partial pressure of the gas and n and k are constants. The constant k is the static or the equilibrium adsorption capacity and plays an important role in designing hold-up systems.

(b) The degree of adsorption depends on the critical temperature and boiling point of the adsorbate. Gases with low critical temperatures, such as noble gases, show a volatility at room temperature which exceeds the attraction forces of the adsorbent, hence the increase in the adsorption efficiency on refrigerating.

(c) The extent of adsorption also depends on the surface area of the adsorbent. The total surface per unit mass of activated carbon can be as much as $1000 \text{ m}^2 \text{ g}^{-1}$. Nevertheless, in constructing a trap one has also to consider the effects of channelling through the trapping bed, the importance of the size, packing and geometry of the adsorbent and trapping bed (Bernard, Foltz, Stoker and Roberts 1958, Browning 1960).

2.2. Adsorbent selection

There are several types of adsorbents available, including activated charcoal, silica gel and molecular sieves. However, it has been reported that activated charcoal is the most effective adsorbent for this particular application (Browning, Adams and Ackley 1959).

In order to investigate the dynamics of activated charcoal relative to ^{133}Xe adsorbate, several tests were performed with glass columns, 250 mm long and 18 mm inner diameter, packed with various types of charcoal. Each column was connected to an air pump for maintaining a continuous sweep gas flow and mounted under a scintillation camera. ^{133}Xe was then injected as a pulse in front of the glass column and the adsorption behaviour was studied dynamically for each type of charcoal by using a scintillation camera. From these simple tests it was easy to select the charcoal with the best retention for our purposes. It was observed that optimum results were achieved with the charcoal Picatif G 210 (Pica, France).

2.3. The kinetic model for adsorption

Several mathematical models have been suggested to describe the dynamics of the adsorption process (Kenney and Eshaya 1960, Burnette, Graham and Morse 1961, Madey 1961, Kovach 1970, Underhill 1970). One of the most successful equations is Browning's Theoretical Chamber Model (Browning and Bolta 1956). This model assumes that the charcoal bed consists of finite sections called 'chambers' connected in series and occupying the total volume of the trap. When the gas enters a chamber it is assumed to be instantly spread and brought to adsorption equilibrium throughout the entire theoretical chamber. Although the physical basis for this model can be questioned, the model itself corresponds to actual experimental conditions with surprising accuracy.

Browning and Bolta (1956) derived the following expression for the partial pressure of the radioactive gas in a particular chamber N , following an injected pulse of radioactivity:

$$-\frac{dP_N(t)}{dt} = \frac{FN P_N(t)}{km} \quad (2)$$

where $P_N(t)$ is the partial pressure of the radioactive gas in chamber number N , F is the flow rate of the sweep gas, k is the dynamic adsorption capacity and m is the mass of the charcoal. The solution of N such differential equations yield the partial pressure in chamber N as

$$P_N(t) = \frac{N^N B F^{N-1} t^{N-1}}{(N-1)! (km)^N} \exp\left(-\frac{N F t}{km}\right) \quad (3)$$

where B is the amount of radioactivity injected into the first theoretical chamber and t is the time elapsed from the pulse injection.

Since the product of the partial pressure and the flow rate of the sweep gas describes the activity release per unit time, eqn (3) describes the rate of radioactive removal from chamber N .

From the above equations two important parameters can be obtained: (i) the dynamic adsorption capacity, k , which characterizes the hold-up time interval, and (ii) the number of theoretical chambers N for a given trap geometry which dictates the release of the effluent activity.

$$k = t_{\max} \frac{NF}{(N-1)m} \quad (4)$$

$$N = \frac{\ln(P(t)/P_{\max})}{\ln(t/t_{\max}) + 1 - (t/t_{\max})} + 1 \quad (5)$$

where $t_{\max}$ is the time taken to attain maximum rate of radioactivity release, $P_{\max}$ the corresponding partial pressure in the last chamber and $P(t)$ the partial pressure at time t .

2.4. Measurements of adsorption kinetic parameters

In order to evaluate the dynamic adsorption capacity k and the number of theoretical chambers N for different situations, the following experiments were performed.

Footnote: Equation (3) should be: $P_N(t) = \frac{N^{N-1} B \cdot F^{N-1} t^{N-1}}{(N-1)! \cdot (km)^{N-1}} \exp\left(-\frac{NFt}{km}\right)$

The charcoal Picatif G 210 was packed tightly in two types of brass pipes with 16 and 37 mm inner diameter respectively. The length of the pipes was varied between 0.25 and 3.5 m (see fig. 1).

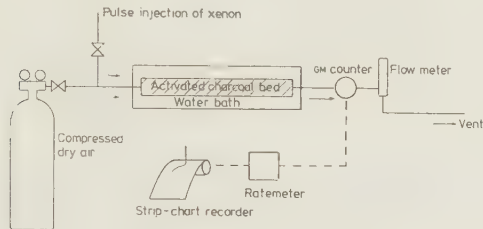


Fig. 1. With the sweep gas flowing, a xenon pulse is injected at the front of the charcoal bed. The activity released from the trap is detected by the GM counter and displayed by the strip-chart recorder.

^{133}Xe was injected as a pulse into flowing dry air and passed through the charcoal bed. The effluent activity was measured with a GM counter connected to a ratemeter and a strip-chart recorder. This procedure was adopted for each trap geometry at three temperatures, 10, 20 and 30 °C, and for each temperature at four sweep gas flow rates, 1.3, 3.4, 6.7 and 10.5 l min⁻¹ (a total of about 50 experiments). All measurements were corrected for countloss due to the dead time of the GM tube. The count rate thus obtained is assumed to be proportional to the partial pressure of xenon at the point of measurement.

3. Results and discussion

3.1. Selection of optimum adsorbent

The recorded data from the scintillation camera measurements were evaluated in the following manner. A region of interest was chosen for each glass column, covering 20 cm of the total column length and beginning at the front of the glass column. The clearance rate of the activity present in this area after the pulse injection of ^{133}Xe was used as a selection guide. Fig. 2(a) shows the behaviour of four types of charcoals, Picatif G 210, Picatif GX 180 and two from KEBO (Stockholm, Sweden) of grade 0.5–1 mm and 2–3 mm respectively, measured at a flow rate of 15 l min⁻¹ at 20 °C. From this figure, and from data available for other rates of flow and temperatures, it can be deduced that charcoals G 210 and GX 180 yield optimum results with a slight preference in favour of G 210. Therefore, G 210 was selected for further experiments. The dynamic responses of G 210 and GX 180 are demonstrated in fig. 2(b), where the activity distribution within the glass column is isometrically displayed at the time of xenon injection and 5 and 20 s later.

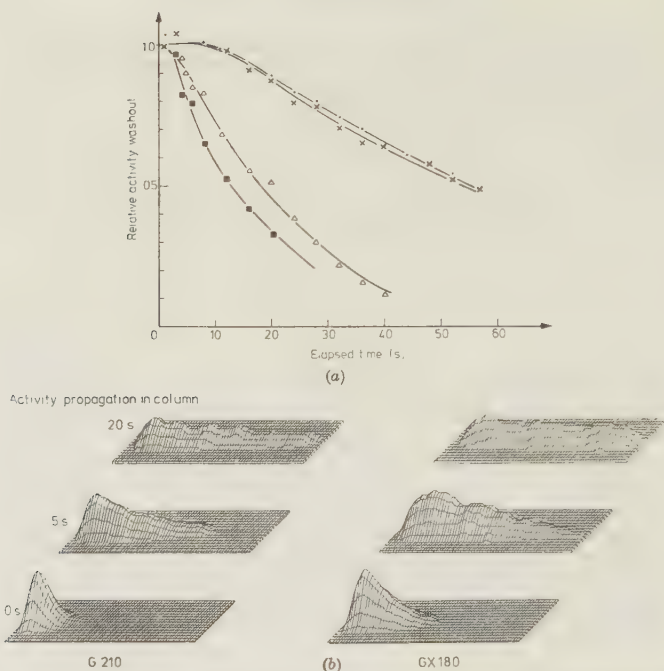


Fig. 2. (a) Relative activity washout for different types of charcoals, packed in glass columns with 18 mm inner diameter. Data are taken from a region of interest, covering 20 cm of the columns. ●, G 210; ×, GX 180; △ and ■ represents common charcoal types, grade 0.5–1 mm and 2–3 mm respectively. Flow rate is 15 l min^{-1} and the temperature is 20°C . (b) Isometric display of activity propagation in glass column for the charcoal types G 210 and GX 180. The activity distributions are shown at the time of injection, 5 s and 20 s later. The flow rate is 15 l min^{-1} and the temperature is 20°C .

3.2. Quantitative studies of Picatif G 210

The data on activity release as a function of time for different trap geometries were used to fit the mathematical model. By using eqn (5) one can calculate a set of N values for a given trap geometry and apply the mean value as the theoretical number of chambers in the trap. One also obtains the dynamic adsorption capacity k from eqn (4), and by substituting these values of N and k the theoretical expression (3) can be solved. The deviations of N and k about their mean values have been small in almost all cases. In all measurements we

have noted excellent agreement between theory and experiment and in about 10% of all measurements no discrepancies could be observed at all. Fig. 3 shows a representative situation of activity released with a slight discrepancy between theory and experiment at the later part of the curve. This discrepancy

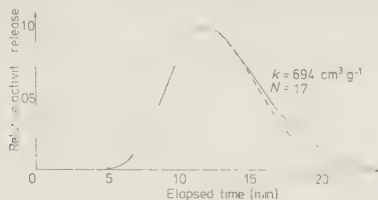


Fig. 3. Typical activity release curve as a function of elapsed time from injection of the xenon pulse. The straight line shows experimentally measured activity released from a 193 g, 16 mm diam. trap. The theoretical predictions are represented by the dashed line. No discrepancy occurs in the first part of the figure. The flow rate is 10 500 cm³ min⁻¹.

occurs because only the first part of the experimental curve is used for deriving the parameters k and N . This procedure was adopted to derive a mathematical tool of high precision and accuracy which would predict the first release of activity from the charcoal trap.

The dynamic adsorption coefficient k is approximately proportional to $\exp(1/T)$, where T is temperature in K. The real situation is depicted in fig. 4. One can observe that changing temperature from +10° C to +30° C results in a reduction of adsorption capacity by a factor of 2.

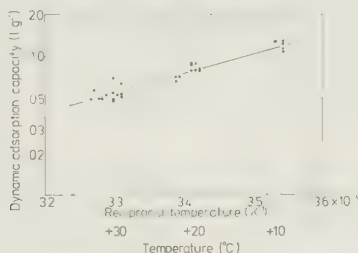


Fig. 4. The dynamic adsorption capacity as a function of the reciprocal temperature.

Both N and k are important parameters for describing the trapping characteristics. From eqn (4) it is obvious that the mean hold-up time period depends on k . The number of theoretical chambers, N , describes the form of the activity release curve. A small value of N produces a broad, flattened curve, while a larger N results in a sharp activity release.

To summarise the results from all measurements, we have calculated the amount of radioactivity released within a fixed time t_0 for different trap geometries. For a given trap we obtain the net fractional radioactivity released within time t_0 as

$$\begin{aligned}\text{Fraction released} &= \int_0^{t_0} FP_N(t) dt \bigg/ \int_0^\infty FP_N(t) dt \\ &= \int_0^{t_0} t^{N-1} \exp(-FNt/km) dt \bigg/ \int_0^\infty t^{N-1} \exp(-FNt/km) dt.\end{aligned}$$

This equation can be simplified by rewriting the infinite integral in terms of the gamma function. Thus, we have

$$\text{Fraction released} = \{FN/km\}^N \int_0^{t_0} t^{N-1} \exp(-FNt/km) dt \bigg/ \Gamma(N). \quad (6)$$

This expression can be solved easily by using Simpson's rule if the relationship between N and m , the mass of the charcoal, is known.

Present measurements indicate that a linear relationship exists between the number of theoretical chambers N , and the mass of the charcoal, m . However, the pipe diameter determines the constant of proportionality. We used the following expressions relating N and m at the flow rate 10.5 l min^{-1} :

$$N = 0.06 m, \quad \text{SD} = \pm 0.01 m, \quad 37 \text{ mm diam. pipe,}$$

$$N = 0.11 m, \quad \text{SD} = \pm 0.02 m, \quad 16 \text{ mm diam. pipe.}$$

Browning and Bolta (1956) suggested a hypothesis in which N varies inversely with pipe diameter. In fig. 5 we have plotted N as a function of m/d , where d is the pipe diameter. A linear relationship appears to exist and thus the diagram can be used for interpolating to other pipe diameters.

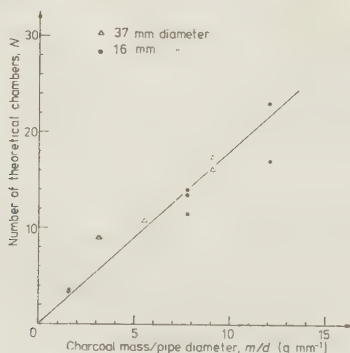


Fig. 5. Number of theoretical chambers, N , as a function of charcoal mass divided by pipe diameter. Flow rate is 10.5 l min^{-1} .

We have not made any corrections for temperature dependence of N . Such a dependence appears to exist but is almost negligible. A realistic estimation of this dependence within the temperature range 10–30 °C is a reduction of N by approximately 0.5% per degree of temperature increase. N is, however, very sensitive to the flow rate of the sweep gas. As can be seen from fig. 6,

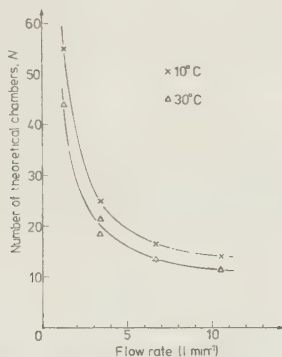


Fig. 6. Number of theoretical chambers, N , as a function of sweep gas flow rate. The figure shows the situation for a 125 g, 16 mm diam. trap at +10 °C and +30 °C.

there is initially a marked reduction of N when changing from small to large flow rates of the sweep gas. This is probably caused by increasing channelling effects through the trapping bed. We also see in fig. 6 that the rate of decrease of N drops rapidly for larger flow rates. Thus, the analytical expressions for N and m above are approximately correct in practice even for flow rates exceeding 10.5 l min⁻¹.

One important aspect that must be considered is the effect of charcoal packing on N . Browning *et al.* (1959) have shown that even a rather small void in the trap causes a decrease in N . It is therefore important to have the maximum charcoal density in the trap. The first trap for real use was constructed for a maximum purification capacity of 100 l at a sweep gas flow rate of 10 l min⁻¹; thus, a process time of 10 min is achieved. The working temperature chosen does not exceed +30 °C, allowing the trapping to occur at room temperature. In order to demonstrate the release of activity from such a trap as a function of charcoal mass, we have plotted eqn (6) in fig. 7. The trap is assumed to work for ten minutes at a flow rate of 10.5 l min⁻¹. An increase in the amount charcoal causes a rapid increase in trapping efficiency. With a 50 g charcoal bed almost all activity will be released within ten minutes while a 350 g bed only releases 0.1%. Data shown are for the 37 mm diameter pipe at 20 °C.

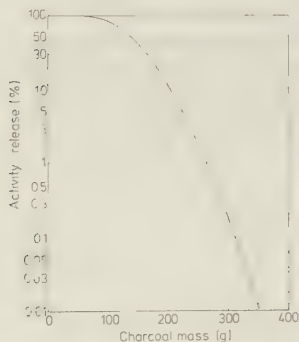


Fig. 7. Fraction of released activity within ten minutes as a function of charcoal mass in the trap. The figure is for the 37 mm diam. pipe at $+20^{\circ}\text{C}$.

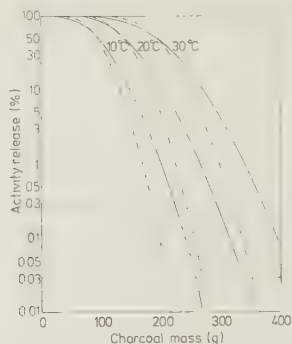


Fig. 8. Fraction of released activity within ten minutes as a function of charcoal mass in the trap at three temperatures, 10, 20 and 30°C . The dashed lines represent the 16 mm diam. trap and the straight lines the 37 mm diam. trap.

The effect of different temperatures on trapping efficiency is shown in fig. 8 for both trap geometries. There is a large difference in trapping efficiency between 10 and 30°C . The effect of small N values for the thick pipe relative to the thin pipe is also demonstrated. For the same trapping efficiency the thicker pipe thus needs more charcoal than the corresponding thinner one.

Before constructing a trapping system by using data from figs 7 and 8 it must be realised that these diagrams correspond to the situation when all the xenon is supplied to the trap as a single pulse. In reality, the xenon will be

supplied continuously and the figures are, therefore, overestimating the released fraction. We have also ignored effects caused by the discrepancy in the tail of the activity release curves mentioned earlier. This would not, however, effect the basic features of figs 7 and 8.

From these curves we constructed the first prototype trapping system consisting of 450 g charcoal packed into a 37 mm diameter brass pipe. According to the figures, this trap will release far less than 0.1% of the injected activity within ten minutes at a temperature of +30 °C. Because of the upper limits depicted in these figures the activity release will be even less than 0.1%, as has been verified experimentally.

To re-use the xenon, the trapped activity must be released and pumped into the spirometer. This process must be done quickly in order to confine the activity in as small volume as possible. We have taken five litres to be the maximum volume of the released xenon gas. By using eqn (4) and the exponential variation of the dynamic adsorption capacity relative to the reciprocal temperature, one can calculate an approximate temperature of the charcoal for maintaining such a rapid release. Calculations show that the charcoal temperature must be of the order of +250 °C to release almost all the activity into a volume of five litres. At this elevated temperature one cannot use compressed air as the sweep gas because of the ignition hazard of the charcoal. The danger of carbon monoxide formation must also be considered if oxygen is present. For these reasons we use high purity nitrogen as the sweep gas. Oxygen is later added to the spirometer. There is still a small risk of carbon monoxide formation due to the presence of oxygen bound to the charcoal. The amount of carbon monoxide in the spirometer was found to be less than 2 mg with any further precautions; this may be compared to the amount of carbon monoxide inhaled by smoking one cigarette, which is approximately 15 mg. No other toxic impurities will be present. As a result of the heating, sterilization of the xenon gas and regeneration of the charcoal are achieved.

Regeneration of the charcoal is important since water vapour, carbon dioxide, etc. will reduce the efficiency of the trap (Browning *et al.* 1959). It is also important to dry the exhaled air before letting it into the trap, in order to enhance its lifetime.

In fig. 9 the clinical recycling system is schematically shown. The exhaled air is conducted to a buffer bag with approximately 15 l maximum volume. The air is pumped out of this bag and through a moisture and carbon dioxide absorption system (silica gel and soda lime) and thereafter through the charcoal bed in order to trap the xenon. The decontaminated air stream from the outlet of the charcoal column can be released directly into the laboratory, but in case of leakage it would be safer to release the air via a ventilation system.

In order to minimise the amount of carbon monoxide formed during the warm-up, about 10 l of nitrogen are blown through the charcoal to remove gaseous oxygen, prior to heating the unit. All of the input valves to the charcoal are then closed, and the heating unit is turned on. The output valve, however, is open during heating, in order to release the adsorbed air being de-gassed

from the charcoal. Since the released gases will occupy a volume of approximately 4–5 l and only contain a very negligible amount of the xenon (less than 1%), they are allowed to escape through the ventilation system. When the temperature has reached 250–300 °C, the output valve is switched to the spirometer. About 5 l of nitrogen are then blown through the charcoal bed, the spirometer. About 5 l of nitrogen are then blown through the charcoal bed,

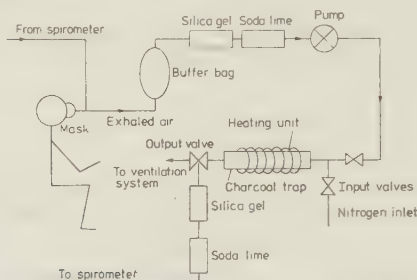


Fig. 9. Schematic diagram of the recycling system. The exhaled air is conducted directly to the buffer bag and pumped through the charcoal bed in order to trap the xenon. To release the trapped activity the heating unit is turned on. When the charcoal temperature has reached 250–300 °C, the output valve is switched to the spirometer and 5 l of nitrogen are blown through the charcoal which is sufficient to return almost all of the trapped xenon to the spirometer,

and this is sufficient to conduct almost all (90–95%) of the xenon away from the trapping bed and return it to the spirometer. Before entering the spirometer the reprocessed gas is filtered through silica gel and soda lime.

From our tests with the prototype trap, we have observed that as much as 95% of the expired activity can be discharged into the spirometer. The total process time is dependent on the heating conditions. We have used a 750 W heating unit which will heat the trap to +250 °C within 15 min. Thus, the total process time, including breathing, is approximately 25 min but can easily be shortened.

Using the theoretical equations given and the experimentally determined parameters, it is possible to construct a system with any arbitrary capacity.

The prototype system is now in use at the Department of Psychiatry, Lasarettet, Lund, for recycling ^{133}Xe during cerebral blood flow measurements. Excellent results have been obtained; the recycling efficiency is normally in the range of 90–95%. The economic benefits are obvious. A preliminary calculation shows that the annual cost for ^{133}Xe can be reduced by 50%. If ^{127}Xe is to be used on a large scale, re-use is essential, purely on cost considerations.

The second prototype is now being developed in order to get an automatic recycling unit suitable for typical clinical situations (a report on this system will be published later by Bolmsjö, Lange, Persson and Simonsen). It is felt

that this system will meet a pressing need, especially for those clinics with a large consumption of xenon gas.

We would like to thank K.-Å. Carlsson for setting up our experimental apparatus, J. Risberg, Department of Psychiatry, Lasarettet, Lund, for valuable help in the clinical tests, I. Balog for analysing the recovered material and E. von Sabsay, Isotronic AB, Täby, for supplying us with charcoals.

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RÉSUMÉ

Système de piégeage et de réutilisation de xénon radioactif en médecine nucléaire

Description de différentes méthodes de piégeage du xénon radioactif. La méthode par adsorption sur charbon de bois activé a l'avantage d'être simple et économique et également de permettre de recycler le xénon. Description d'un système de piégeage sur charbon de bois activé qui peut extraire ^{133}Xe à partir de 100 litres d'air expiré en 10 min par des malades qui font l'objet d'études de circulation ou de diagnostic pulmonaire. Examen des détails de la construction. Le gaz enfermé peut être rapidement libéré et renvoyé au spiromètre. L'on peut obtenir une réduction nette des coûts avec ^{133}Xe ; cela présentera une importance croissante à mesure que les ^{137}Xe produits par accélérateur deviendront de plus en plus courants.

ZUSAMMENFASSUNG

Auffang- und Wiederverwendungssystem für radioaktives Xenon in der Nuklearmedizin

Verschiedene Methoden zum Auffangen radioaktiven Xenons werden diskutiert. Auffangen durch Adsorption aktivierter Holzkohle hat den Vorteil, dass diese Methode einfach und billig ist und die Wiederverwendung des Xenons erlaubt. Ein Auffangsystem, bei dem aktivierte Holzkohle verwendet wird, wird beschrieben. Bei Patienten, die diagnostischen Lungen- und Kreislaufuntersuchungen unterzogen werden, kann hiermit innerhalb von 10 Minuten aus 100 Litern ausgemessener Luft ^{133}Xe gewonnen werden. Einzelheiten des Systems werden erläutert. Das aufgegangene Gas kann unverzüglich freigesetzt und dem Atmungsmeßer wieder zugeführt werden. Durch ^{133}Xe kann eine beträchtliche Kostensenkung erreicht werden; dieser Faktor gewinnt dadurch sogar noch mehr an Bedeutung, weil durch Beschleuniger erzeugtes ^{137}Xe immer größere Verwendung findet.

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A NEW INSTRUMENT FOR SURVEY MONITORING OF AIRBORNE XE-133.

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ABSTRACT

Methods for measuring Xe-133 contamination of the air in medical clinics are reviewed. The principles of a new, simple and low cost monitor are outlined. Results from experimental tests in laboratories and medical clinics were encouraging, indicating that the monitor is a valuable tool for survey measurements of Xe-133 contamination in nuclear medicine departments.

1. INTRODUCTION

In the clinical use of Xe-133 radioactive tracers, it is in actual practice impossible to avoid spreading of the isotope to the laboratory air (LeBlanc and Johnson, 1975, Bolmsjö, 1981). The MPC-value (Maximum Permissible Concentration) for Xe-133, 0.37 MBq/m³, has previously been used to express the mean air concentration of airborne xenon that gives maximum permitted dose equivalent for occupational exposure (ICRP Publication 2, 1959). New information on the effects of radiation on the body has necessitated recalculations of the MPC-values. It has then been shown that the old limit for Xe-133 was too pessimistic (ICRP Publication 30, Parts 1 and 2, 1979, 1980) The MPC-concept has now been replaced by the new DAC, Derived Air Concentration. For Xe-133, 1 DAC is 4 MBq/m³ for an infinite room and 20 MBq/m³ for a room size of 100-1000 m³ in volume.

If potential risks for high levels of activity leakage exist, e.g. at the handling of 37 GBq ampules, it is advantageous to have some form of xenon-detecting system. This ensures a proper working environment for the staff.

A common method to detect Xe-133 contamination of the air in the laboratory is to continuously pump room-air through an

open ionization chamber. The ionization current from the detector is then a figure of the Xenon gas-concentration in the air. Commercially available monitors based on this or similar techniques, cost around 1,000 - 1,500 pounds sterling.

In order to have a cheaper alternative for survey of the laboratory air, several authors have suggested other methods for measuring air contamination of Xe-133. Among these is direct measurement of the room radiation by an uncovered scintillation detector (Rudin and Hart, 1971). Such an approach can, however, suffer from inaccuracy due to uncertainty about the amount of radiation detected that is related to air contamination, and which amount emanates from other sources (e.g. the patient being investigated).

Recently, two papers have been published based on air samples taken with

- 1) Evacuated 10 cc tubes, and
- 2) Small tubes (5 ml) filled with activated charcoal.

The samples were afterwards measured by means of a stationary scintillation detector (Jacobstein, 1979; LeBlanc et al., 1979). Both these methods are, however, non-continuous measuring techniques.

Xenon atoms which are brought in contact with activated charcoal are adsorbed on the surface of the charcoal. The binding is weak (Van der Waal forces) and the Xenon is therefore not permanently trapped (Bernard et al., 1958). A continuous exchange between adsorption and desorption of Xenon atoms occurs. When a Xenon-contaminated air stream is pumped through a tube filled with activated charcoal, those Xenon atoms which are temporarily desorbed are carried forward by the air flow until they are again adsorbed or breakthrough at the effluent side eventually occurs. By this process, passage of the Xenon through the charcoal bed is slowed down. The net effect is that the concentration of

Xenon in the charcoal is several orders of magnitude higher than in the surrounding air. At the low partial pressures of Xenon present in nuclear medicine applications, one gram of a typical noble-gas adsorbing charcoal type has the capacity to adsorb the amount of Xenon that is present in about 0.7 liters of air (at 20°C) (Bolmsjö and Persson, 1981). This property can be utilized to improve the sensitivity of small radiation detectors to also be useful for Xenon leakage-measurements.

By mounting a small GM-tube inside a lead-shielded tube filled with activated charcoal and then connecting the unit to an air pump and an electronic ratemeter, it is possible to obtain a cheap and sufficiently sensitive detector for continuous measurements of Xe-133 air contamination in nuclear medicine departments.

The aim of this paper is to introduce a new monitor for survey measurements of air-borne Xe-133 based on the above described principle.

2. MATERIALS AND METHODS

The Xenon detector system was constructed with a GM-tube (Philips 2P 1400, 5 cm³ detector volume) mounted centrally inside a plexiglass tube, 75 mm in length and with an inner diameter of 34 mm. A 3 mm lead-shield was mounted on the outside of the plexiglass tube in order to shield it from external radiation. The tube was then packed with 25 g of the charcoal type Picatif G210 (Pica, France), which previously has been found to be useful for Xenon adsorption (Bolmsjö and Persson, 1978). A second tube was also tested with 15 g of the same charcoal. An air pump was connected to obtain an air-flow through the charcoal at the rate of 5 litres per minute.

To obtain a complete detector system, the GM-tube was connected to a ratemeter, having a time constant of 1 minute. For testing and calibration purposes, a digital frequency counter was also connected to the GM-tube output.

Calibration of the detectors was performed in a sealed, leakproof 0.21 m^3 large box covered with aluminium foil. Known activities of Xe-133 were conducted into the box via a pump system. Activity concentrations ranging from 0.2 to 60 MBq/ m^3 were used for the calibration procedures. The activities were first absolute-determined in a Ge(Li)-spectrometry system, which in turn was calibrated by a standard source of Xe-133 from the National Physical Laboratory, Teddington, England. During the calibration, the temperature in the box was maintained constant at 20°C . The temperature dependence of the Xe-sensitivity was measured by repeated calibration at 30°C .

The 25 g-charcoal detector was used continuously for about five months at a medical clinic where Xe-133 was being used for a large number of routine patient investigations. Approximately 1000 m^3 of air was pumped through the charcoal during this period. Afterwards, the detector was again calibrated to evaluate the long term stability of the system. For comparative purposes, simultaneous recordings of the room air concentration of Xe-133 were performed on several occasions during the clinical test by using a Xe-133 monitor, based on ionization chamber technique (Xenon Monitor 133C, Johnston Laboratories, Inc., USA).

To obtain a very sensitive Xe-monitor, a NaI-detector ($3\frac{1}{4}'' \times 3\frac{1}{4}''$) was mounted inside a lead-shielded 5 g charcoal bed. It was calibrated in the same manner as the GM-monitor. No energy-discrimination, except for low-amplitude noise, was done.

3. RESULTS

The calibration of the detector containing 25 g of activated charcoal is shown in Figure 1, both for the new, unused charcoal and after 5 months of usage. As can be seen, there is no significant difference in sensitivity between the two calibration occasions. This indicates that the system has a good long-term stability. This is also in agreement with other studies previously reported, which showed that deterioration of charcoal due to long-term usage and aging is minimal (Siegwarth et al., 1972; Bolmsjö and Persson, 1981). A Xe-133 concentration of 0.4 MBq/m^3 was detected with a net count rate of the same order as the background (15 cpm). There is a clear linear relationship between the room-air Xenon concentration and the GM-tube count-rate. This agrees well with the theory for adsorption of noble gases at low partial pressures on activated charcoal where no saturation effects occur. The background was stable during the entire test-period. To quantify the role of the charcoal, a measurement was carried out without any charcoal in the plexiglass tube. It was found that the sensitivity of the GM-tube then was reduced by a factor of 40.

Only a minor difference in sensitivity between the 15 g- and the 25 g-charcoal tubes was observed. The 15 g-tube was 15% less sensitive than the 25 g-tube, whereas it could be expected that the sensitivity should vary as the ratio of the charcoal masses. The smaller difference observed is due to the attenuation of the gamma- and X-ray-radiation from Xe-133: thus the Xenon adsorbed in close proximity to the GM-tube makes the largest contributions to the signal. No beta-particles are detected since they are already absorbed within the charcoal.

Typical recordings of the Xe-133 leakage into the room-air at the medical clinic investigated are shown in Figures 2a and b. Figure 2a shows the measurements made by the pre-

sented system and Figure 2b is the simultaneous measurement made with the ionization chamber detector. As can be seen, the agreement between the two systems is very good. The peaks in the figures correspond to the activity leakage at each patient investigation during the measurement period. With the scintillation detector, a Xe-133 concentration of 40 kBq/m^3 was detected with a net count rate of the same order as the background (100 cpm).

4. DISCUSSION

The simplicity of the described instrument makes it suitable for survey measurements of Xe-133 leakage in medical clinics. By using a standard GM-counter and fitting it with a charcoal filter and an air-blower, a cheap instrument is obtained at a cost of 20-30% of that for regular Xenon monitors. The least detectable sensitivity was around 0.4 MBq/m ($1/10 - 1/50$ of DAC) with direct analogue read-out (moving coil instrument). If a digital event-counter, i.e. a scaler, is used, the least detectable limit could, however, be brought down to below 0.1 MBq/m^3 , with acquisition times of 20 - 30 minutes. Use of a scaler further enables integration of the air-concentration over an 8-hour period. A simple frequency-counter will be useful for this application. The scintillation-detector instrument was about ten times more sensitive than the GM-instrument, which is due to the large inherent detection efficiency of a NaI-crystal. With acquisition times of half-an-hour, the least detectable limit can be brought down to below 10 kBq/m^3 . For charting of activity levels in non-occupational areas outside the laboratory, the NaI-detector approach is therefore preferable. An even more sensitive instrument would result if a small well-crystal is used with the charcoal packed in the well. The measuring geometry is then almost 4π .

The charcoal chamber must be properly shielded in order to avoid erroneous recordings due to external radiation from other isotopes. The overall time constant of the instrument is partly dependent on the rate the adsorbed Xenon is exchanged with the surrounding air. This is a function of the charcoal mass divided with the flow-rate of the air pump. For the charcoal tubes and flow-rate used in this study, the time constants were between 2 and 4 minutes. In actual practice, this long time constant was not considered to be a disadvantage, since the concentration levels of Xe-133 in the laboratory air also vary slowly. The monitor responded to activity leakage as quickly as the ionization chamber instrument ($\tau_{\text{ion-ch.}} = 30$ seconds) although the true Xe-concentration from a short release was not immediately readable. With the NaI-based instrument, only 5 g of charcoal was used and the inherent time constant was therefore about 1 minute.

The calibration into activity-concentration units was stable during the entire experimental series, which included long-term usage. The calibration was, however, obtained at a constant temperature of 20°C, and is therefore restricted to this temperature to be valid. It is well known that the adsorption capacity of charcoal is dependent on temperature (Browning et al., 1959). A lowered temperature increases the capacity and the opposite takes place if the temperature is raised. A variation in the ambient temperature with 10°C from the specified 20°C caused a calibration error of a factor of 1.2. In practice, this is seldom a serious drawback since the temperature at a medical clinic is usually constant. A calibration uncertainty of this order is usually acceptable for this kind of instrumentation and often observed even for rather expensive devices. By adding an amplifier with a temperature-dependent gain to the ratemeter output, e.g. by using a thermistor as the gain-determining element, it is possible to correct for this calibration error. Since the detector essentially measures gamma-radiation, Xe-isotopes with a high photon-yield, e.g. Xe-127, should be easily detected.

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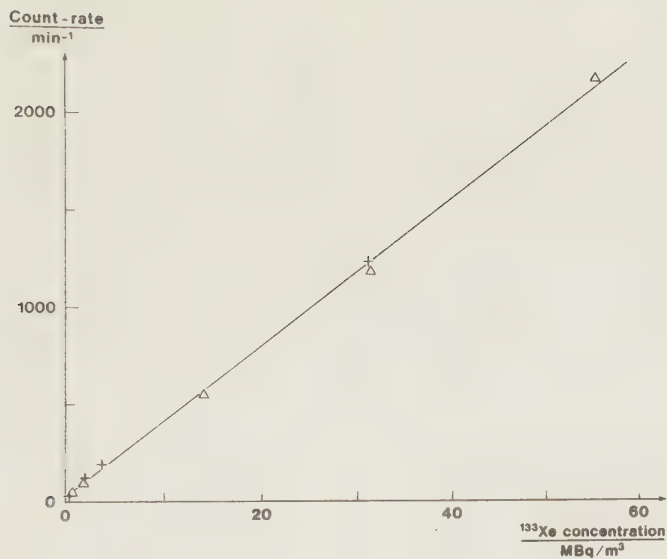
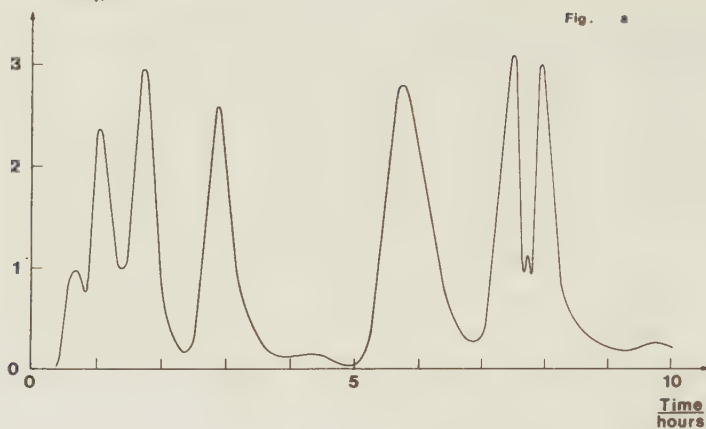


Fig.1. Calibration diagram for the 25 g charcoal detector. The + -dots represent the calibration of the new and unused charcoal, while the Δ -dots are the calibration performed after 5 months of continuous usage.

^{133}Xe room air concentration
MBq/m³



^{133}Xe room air concentration
MBq/m³

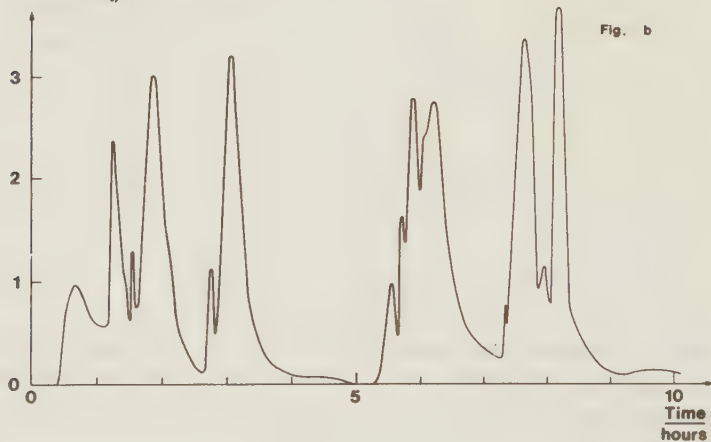


Fig. 2(a,b). Recordings of the air activity of Xe-133 at a nuclear medicine department during a day with extensive use of xenon. Figure 2a shows the recording made by the described system and Figure 2b is the recording of an ionization chamber (Xenon Monitor 133C, Johnston Laboratories, Inc., USA). The peaks in the figures correspond to the leakage into the room-air at each patient investigation. The recordings were made at a distance of 2 m from the patients.

HEMISPHERE CROSS-TALK AND SIGNAL OVERLAPPING IN BILATERAL
rCBF-MEASUREMENTS USING Xe-133.

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1. Introduction

Overlapping and signal-contribution from tissues outside the region-of-interest are well-known problems in nuclear medicine investigations. In regional cerebral blood flow measurements (rCBF) with multidetector set-ups, each detector views a regional volume of grey and white matter (1,2,3). When xenon is administered by inhalation or by i.v. injection, the activity is distributed to the entire brain. Each detector therefore measures radiation originating from both the ipsilateral- and the contralateral hemispheres. Cross-talk is defined as the fraction of the total observed count rate which originates from the contralateral hemisphere (3,4,5,6). The fact that Compton scattering of the 81 keV gamma-radiation from Xe-133 can only be partially discriminated against, and since large-hole collimators are commonly used at rCBF-laboratories, it is necessary to expand the concept of signal-superpositioning to also include contribution from overlapping regions within the ipsilateral hemisphere itself. In the following text, hemispheric cross-talk and overlapping are treated together as "extra-regional signals".

The washout of xenon from the brain has two main components, one that is fast, representing grey matter flow and one that is slower, representing white matter flow. Influence from extra-regional parts of the brain having different perfusion rates, introduces uncertainties in the assessments of the regional grey- and white-matter flows. When a biexponential model is used to describe the washout of xenon, the calculation of the regional grey matter perfusion is mostly influenced by contribution from extra-regional fast components.

The aim of the present investigation was to evaluate the magnitude and effects of extra-regional signals in the calculation of regional grey matter blood flow. For this purpose, a computerized simulation technique was developed.

2. Materials and Method

Detector characteristics

Three-dimensional response functions were recorded for a $3/4" \times 3/4"$ NaI-detector provided with two different collimators. The collimators were lead-cylinders; 17 mm inner-diameter, 21 mm in length, and 10 mm inner-diameter, 36 mm in length, respectively. The detector response-functions were obtained in matrix-form by step-wise scanning a 1 ml cubic source of Xe-133, submerged in a water bath, in front of the detector, see Figure 1. The source displacement between each measurement was 1 cm. For each position, the net count rate per unit activity was taken as the detection response. The sizes of the response matrixes were 29 cm in width, 13 cm in height and 19 cm in depth, giving a total of 7163 elements in each. Due to symmetry, only one quadrant in each matrix had to be determined. For each matrix, 336 elements were measured experimentally and the remaining values in a quadrant (1659 elements) were obtained by interpolation. The matrixes were stored on a mini-computer (PDP 11/45) as disc memory files. Due to the almost identical attenuation coefficients for brain tissue and water at 81 keV, it was assumed that the matrixes also represented the detector responses in brain tissue (7).

The cubic source used was made of 2 mm plexiglass and filled with 1 ml, 1 - 10 MBq of Xe-133 in solution. During the measurements, checking was done every two hours to correct for eventual loss of xenon from the source. The water in the bath was frequently shifted in order to avoid increased background level from diffused xenon being dissolved in the water. The dimensions of the water bath were 25 x 25 x 25 cm³. The wall material was 2 mm thick plexiglass on the detector side and 6 mm in thickness on the other sides. The gap between the detector and the first row of the response matrix was 12 mm including the wall material.

The detector was connected to a multichannel analyzer (Nuclear Data ND100) for data acquisition. The data was registered in two energy intervals, 50 - 110 keV and 66-96 keV, respectively, and corrected for background. A maximum count rate of 5000 per second was allowed in order to minimize disturbance from pile-up and electronic dead-time. All measurements were, however, acquired in live-mode, to automatically correct for dead time losses. The net number of counts registered was larger than 10,000 for all source positions close to the detector and between 300 - 10,000 for the distant positions. The background was in the order of 50 counts.

Brain Model

Anatomical and CT-scan cross-sections of the head were used to define grey and white matter contours of the entire brain (8). The tissue contours were first approximated by ellipses. Using the ellipse-curvature as the boundary of the tissues, the brain cross-sections were transformed to voxel maps, each voxel representing either 1 ml of grey or 1 ml of white matter, see Figure 2.

A FORTRAN IV program was developed to create a three-dimensional model of the brain by "packing" the voxel maps onto each other. A total number of 11 maps were used in this procedure. Two different brains were modelled, 130 x 110 mm and 170 x 150 mm in size, respectively, see Figure 3. The amount of simulated grey matter in each brain was 66% and 62%, respectively. The total voxel-volume was 0.85 and 1.6 dm³, respectively.

The brain models were divided into three different parts, one representing a region-of-interest viewed by a simulated detector, one part representing the remaining extra-regional tissue in the ipsilateral hemisphere, and the third part representing the entire contralateral hemisphere. The region-of-interest was located centrally over one hemisphere. Two sizes of the region-of-interest were chosen, 3 x

3 cm² and 5 x 5 cm², respectively, see Figure 3.

The voxels representing grey matter were then assigned the value '1' to simulate equal concentration of xenon in the cerebral cortex, while the "white matter" voxels were assigned the value '0', i.e. zero activity. By multiplying each voxel with the corresponding element in the detector response matrix and summing the products inside each part of the brain model, the magnitudes of regional- and extra-regional grey matter signals were obtained. The same procedure was adopted for the white matter. In the computerized model, it was possible to move the simulated detector to different positions over the brain. Its actual position was used to define the coordinate offsets between the two matrix systems.

With the described procedure, six coefficients, D_i , appeared, representing the measured signal strength per unit activity-concentration from each part of the brain model. Three of the coefficients represented: 1) the signal from the regional grey matter, 2) from the remaining grey matter in the ipsilateral hemisphere, and 3) from the grey matter in the contralateral hemisphere. The other three coefficients represented the signal strength from the corresponding white matter areas. The coefficients were then multiplied with the estimated xenon concentration in each part of the brain in order to obtain the total signal measured by the simulated detector.

The xenon concentration in the voxels was therefore calculated for different blood flows according to (9):

$$C_i(t) = f_i \cdot \exp\left(-\frac{f_i \cdot t}{\lambda_i}\right) \cdot \int_0^t C_A(\tau) \cdot \exp\left(\frac{f_i \cdot \tau}{\lambda_i}\right) d\tau \quad (1)$$

where $C_i(t)$ is the activity concentration in voxel i , f is the specific blood flow (ml/min/g), λ is the partition coefficient and $C_A(t)$ is the arterial blood concentration of xenon. In this study, the values 0.8 and 1.5 were used for the partition coefficient of grey and white matter, respec-

tively (10).

The activity concentrations in the voxels, $C_i(t)$, were calculated by using a standard inhalation rCBF air-curve to represent the arterial input concentration $C_A(t)$, see Figure 4.

Four blood flow situations were simulated; two with a low region-of-interest grey matter flow of 0.6 and 0.5 ml/min/g, respectively, and two with a high regional blood flow of 1.0 and 1.2 ml/min/g, respectively. The other parts of the brain were assumed to have normal blood flow values, according to Ingvar et al. (11). The extra-regional grey- and white-matter blood flows were therefore chosen as 0.8 ml/min/g and 0.2 ml/min/g, respectively, in all simulations.

The voxel concentrations of xenon were calculated with 5 seconds' intervals from 0 - 12 minutes after start of the simulated inhalation. The xenon-concentrations thus obtained were multiplied with the corresponding detection coefficient, D_i , and added to give the total detector signal, $H(t)$, as:

$$H(t) = \sum_i^6 D_i(t) \cdot C_i(t) \quad (2)$$

The biexponential deconvolution procedure developed by Obrist et al. (12) was then executed on the obtained wash-out-curve, $H(t)$, thus imitating the actual situation in rCBF-analysis.

$$H(t) = P_1 \int_0^t C_A(\tau) \cdot \exp\left(-\frac{f_g}{\lambda_g}(t-\tau)\right) d\tau + P_2 \int_0^t C_A(\tau) \cdot \exp\left(-\frac{f_w}{\lambda_w}(t-\tau)\right) d\tau \quad (3)$$

where P_1 and P_2 are coefficients. The analysis was started after 2 minutes. From the analysis, the two flow parameters f_g (grey) and f_w (white) were reconstructed. By comparing f_g with the actual preselected grey matter flow in the region of interest, the net effect of the extra-regional sig-

nals could be studied.

Phantom correlation

The accuracy of the brain modeling technique was tested in comparison with phantom studies. The phantom consisted of two halves of a cranium and two brain hemisphere models made of 2 mm vacuum-formed CAB-carbolite plastics; one was filled with water, the other with water and 10 MBq of Xe-133. Hemispheric cross-talk was measured by placing the detector on both sides of the cranium. Introducing the quantities S_1 and S_2 , where S_1 is the signal measured from the ipsilateral (activity) side and S_2 is the signal measured from the contralateral (water only) side, the cross-talk was obtained as $S_2/(S_1+S_2)$. The cross-talk was measured at several detector positions over the skull. The phantom contours were later transferred to voxel maps to enable computer simulation of the phantom measurements by using the same procedure as previously has been described. The computed cross-talk was then compared with the measured data.

3. Results

Detector response function

The detector response functions varied with an order of 10^4 between the most distant and the most closest source position to the detector. The loss of xenon due to leakage from the cubic source was less than 5% per day and could be easily corrected for.

Phantom correlation

The results of the comparison between the cross-talk obtained in the phantom study and the corresponding computer simulations, are shown in Figure 5. As shown by the figure, the agreement between experiments and simulation was within 10%. The ratio of the observed count rates between the fine-hole and the large-hole collimators was 0.07 and the corresponding computer-simulated ratio was 0.06.

Data simulation

The calculated signal strengths, D_i , from the different parts of the brain models are given in Table 1. The table values presume unity concentration of xenon in all voxels and shall be multiplied with the actual concentrations before used. It is still useful to compare them directly since it gives a good illustration of the different signal sources and their relative strengths. With equal concentrations of xenon in all voxels, the grey matter in the region-of-interest contributes only with 17 - 29% to the totally detected signal. The Table 1 also shows that between 40 - 65% of the total detected grey matter signal emanates

from outside the region of interest. For the large-hole collimator, the extra-regional grey-matter contribution is between 47 - 65% and for the fine-hole collimator between 40 - 53%. With the larger region ($5 \times 5 \text{ cm}^2$), the influence from extra-regional grey-matter sources is generally less compared to the $3 \times 3 \text{ cm}^2$ region. Use of a narrow energy-window further reduces the influence from extra-regional sources.

The signal from the white matter in the ipsilateral hemisphere is a factor of 2 - 3 larger than from the contralateral side. The cross-talk, calculated according to the $S2/(S1 + S2)$ -formula, is given in Table 1 and is between 22 - 29%, in good agreement with reports from other researchers (5,6). Total elimination of xenon from the grey matter does not alter the cross-talk significantly, since the pure white-matter cross-talk is also in the order of 25 - 30%. The cross-talk appears therefore to be rather constant during the entire washout sequence. The overall relative sensitivities for each collimator are also given in Table 1. It shows that the fine-hole collimator only detects 4 - 6% of the number of counts obtained with the large-hole collimator.

The effects of extra-regional signals on the flow calculations are shown in Table 2. The results show that a regional flow difference and asymmetry are smoothed and only detected by approximately 50% of their true value. For the situations simulated in this report, the error introduced in the calculation of regional grey-matter flow was found to be between 9 - 42%. The deconvolution procedure was in all cases able to fully reconstruct the white-matter flow to 0.2 ml/min/g. The fine-hole collimator generally gave a better resolution of the regional grey-matter flow, but its low sensitivity makes it of little value for non-invasive rCBF-measurements. The results from the two brain sizes investigated are very similar.

4. Discussion

The presented data show that substantial artefacts are introduced in the calculation of regional grey matter flow when flow asymmetries exist. The fine-hole collimator investigated has previously been used in conjunction with intra-carotid injection of Xe-133. It is well-known that this administration technique gives better flow resolution than the inhalation-technique. By simulating uptake only in the ipsilateral hemisphere, the influence on the calculated regional grey matter flow was in all cases less than 14%, using this collimator and the same simulation procedure as previously. The model thus gives results that are in agreement with actual observations (13).

The model does not correct for the attenuation in the cranium but since it is a constant factor, it should not influence the results obtained. The skull bone introduces different conditions for Compton scattering than the water bath. The strong correlation found between the model and the phantom studies shows that these factors are of minor importance. In general, the described technique appeared to be very insensitive to random uncertainties in the response-matrixes. Since about 1,000 voxels are added in the modeling procedure, eventual errors are likely to compensate for each other. The small difference in attenuation coefficients between water and brain tissue may cause a slight overestimation of the calculated cross-talk by 10%.

The results obtained show that further work must be done to improve the accuracy of the measuring technique at bilateral rCBF-investigations. A useful application of the described simulation technique is for evaluating and testing new collimators.

Acknowledgements

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3-dimensional response matrix

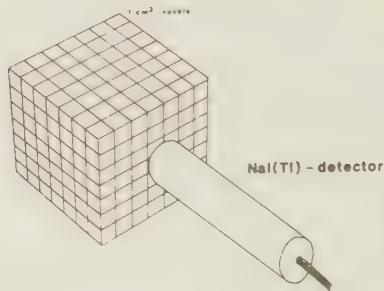


Figure 1: The response-function for a rCBF-detector was measured in a wather bath. Each element in the three-dimensional matrix corresponded to the measured count rate from a 1 cm^3 source of Xe-133 of unity activity.

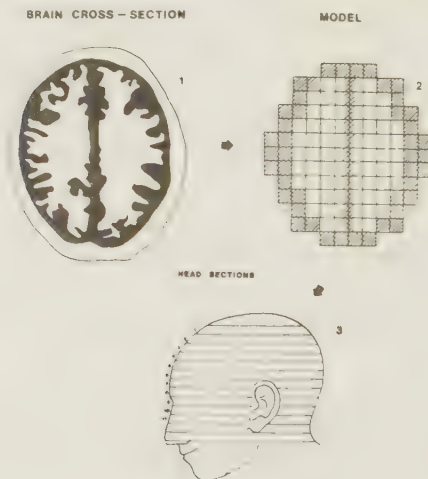


Figure 2: Illustration of the principle that was applied in the modeling of the brain. A set of brain cross-sections, taken from a CT-atlas (Gambarelli et al. 1977), were transformed to voxel maps. Each voxel represented either 1 ml of grey matter (shadowed) or 1 ml of white tissue. The maps were packed on each other to obtain a three-dimensional computer-model of the brain.

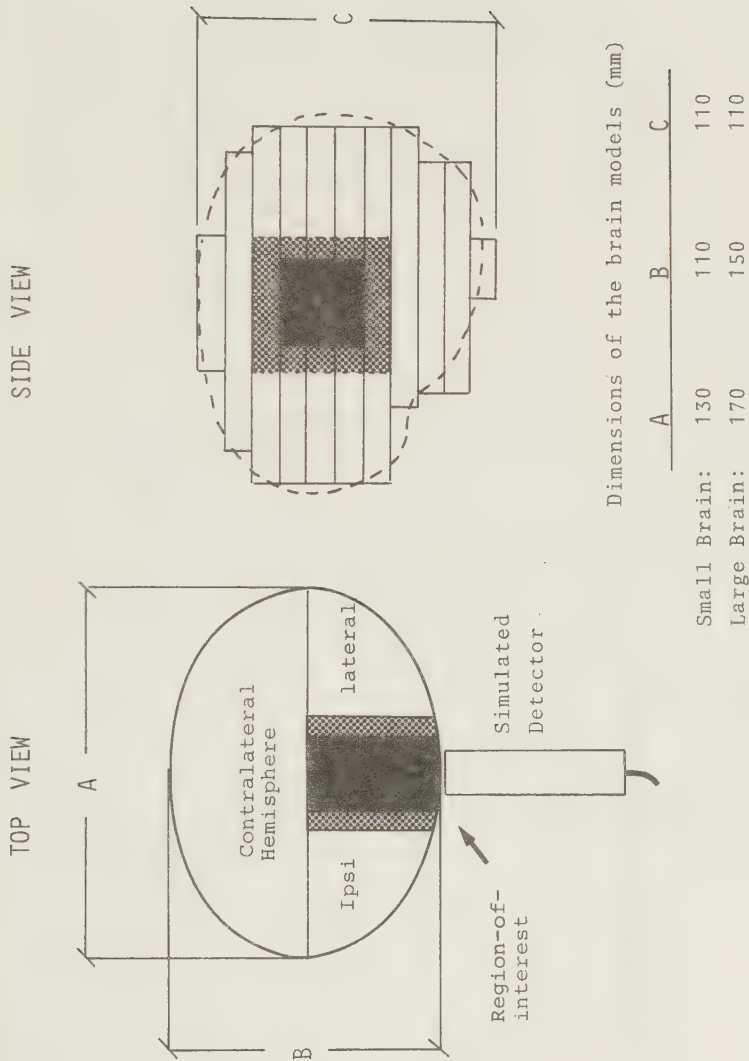


Figure 3: The dimensions of the brain models. The shadowed parts demonstrates the regions-of-interest, above which the simulated detector was located. The frontal area of the regions was $30 \times 30 \text{ mm}^2$ and $50 \times 50 \text{ mm}^2$, respectively.

Xenon Concentration
Arbitrary Units

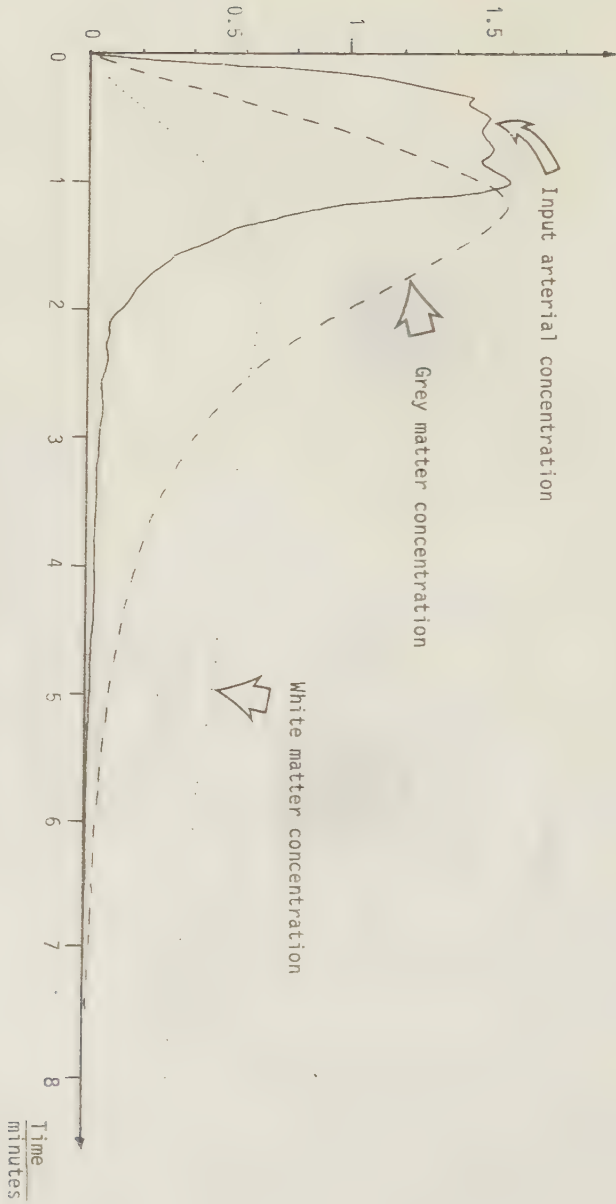
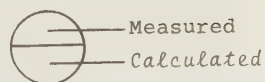
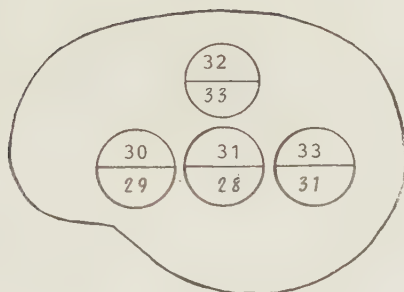


Figure 4: Illustration of the rCBF air-curve used to represent the arterial input function. The resulting grey- and white-matter concentrations of xenon is also depicted.

LARGE HOLE

50 - 110 KEV



FINE HOLE

50 - 110 KEV

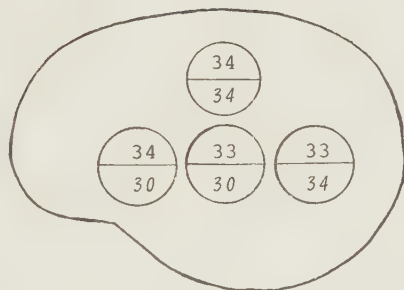


Figure 5 : Comparision of cross-talk between phantom studies and computer simulations.

SIGNAL SOURCES

SMALL BRAIN

GREY MATTER

Collimator	E (keV)	Total signal	Region of interest	Extra-regional		Fraction extra-regional signal
				from ipsilat.	from contralat.	
Large hole	50 - 110	1.0	27% (24%)	13% (16%)	14%	50% (56%)
"	66 - 96	0.68	29% (23%)	12% (18%)	14%	47% (58%)
Fine hole	50 - 110	0.06	28% (24%)	9% (13%)	13%	44% (52%)
"	66 - 96	0.04	29% (26%)	7% (10%)	12%	40% (46%)

WHITE MATTER

from ipsilat.	from contralat.
33%	13%
32%	15%
34%	16%
35%	17%

Classic cross-talk
27%
27%
29%
29%

LARGE BRAIN

Large hole	50 - 110	1.0	22% (17%)	16% (21%)	10%	54% (65%)
"	66 - 96	0.66	24% (19%)	14% (19%)	10%	50% (60%)
Fine hole	50 - 110	0.06	23% (20%)	11% (14%)	9%	47% (53%)
"	66 - 96	0.04	24% (21%)	8% (11%)	9%	41% (49%)

40%	12%
40%	12%
42%	15%
44%	15%

22%
22%
24%
24%

Table 1: Calculated relative signal strengths from the different regions in the two brain models. Equal concentration of Xe-133 in all parts is assumed. The sizes of the region-of-interests are 5 x 5 cm² and 3 x 3 cm², respectively. The values given in the parentheses are for the 3 x 3 cm² region. By adding the signal strengths from the three grey-matter- and the two white-matter- regions, the total (100%) measured signal is obtained.

Collimator	ΔE (keV)	Simulated grey matter flow	Calculated, Small brain	Calculated, Large brain
Large hole	50 - 110	1.2 ml/min/g	0.99 (0.97)	0.97 (0.93)
		1.0	0.90 (0.89)	0.89 (0.87)
		0.6	0.71 (0.71)	0.72 (0.74)
		0.5	0.67 (0.69)	0.68 (0.71)
Large hole	66 - 96	1.2 ml/min/g	1.00 (0.96)	0.99 (0.94)
		1.0	0.91 (0.89)	0.90 (0.88)
		0.6	0.70 (0.72)	0.71 (0.73)
		0.5	0.66 (0.69)	0.70 (0.70)
Fine hole	50 - 110	1.2 ml/min/g	1.01 (0.98)	1.00 (0.97)
		1.0	0.92 (0.90)	0.91 (0.90)
		0.6	0.70 (0.71)	0.70 (0.72)
		0.5	0.65 (0.68)	0.66 (0.68)
Fine hole	66 - 96	1.2 ml/min/g	1.03 (1.00)	1.02 (1.05)
		1.0	0.92 (0.91)	0.92 (0.91)
		0.6	0.69 (0.70)	0.69 (0.71)
		0.5	0.64 (0.66)	0.64 (0.67)

Table 2: Comparison of the simulated grey-matter flows (ml/min/g) in the region-of-interest and the calculated flow. The extra-regional grey-matter flow was 0.8 ml/min/g and the white-matter flow was 0.2 ml/min/g. The values given in the parentheses are for the $3 \times 3 \text{ cm}^2$ region-of-interest.

MEASUREMENT OF BLOOD FLOW IN RAT LIVER WITH XENON-133.

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Abstract

The blood flow in rat liver was measured with Xe-133. Three techniques for administering the activity to the liver were employed: Injection via the portal vein, via the hepatic artery, and directly into the liver parenchyma. Use of intraparenchymal injection of Xe-133 gave 60% higher flow values than by portal or arterial injection techniques. This may be explained by the microcirculatory anatomy of the rat liver.

Presented data have a high degree of variance between repeated experiments on the same animal. During an experimental procedure, only larger changes in the liver blood flow pattern can be detected with sufficient accuracy. For this purpose, the method is applicable since repeated and regional studies on the same organ can easily be performed.

1. Introduction

Blood flow measurements in the liver have been subjected to extensive research with varying techniques. Examples of direct methods that have been employed are drop recording (Folkow, 1953), thermodilution (Gregg, 1948) and electromagnetic flow-metering (Denison et al., 1955). Among the indirect methods to assess blood flow is the usage of freely diffusable tracers. This technique has been widely in use since the mid-1940's when Kety and Schmidt (1945, 1948; Kety, 1951) first described the fundamental principles.

At present, the radionuclide Xe-133 is by far the most commonly used inert gas tracer for organ blood flow measurements. Usually, the radioactive xenon is administered either directly into the tissue or as a bolus injection via the arterial supply. Several methods have been developed to calculate the organ blood flow from the measured washout of

the isotope (Kety, 1960; Zierler, 1965). Exponential analysis is commonly used and is based on the assumption that diffusion equilibrium between the xenon in blood-phase and the xenon in tissue-phase is established within the order of a second or less. The concentration of xenon in the venous blood leaving the organ is therefore in continuous equilibrium with the tissue concentration. The gas is thus transported from the tissue in question at a rate which is proportional to the nutritive blood flow (Kety, 1960). It finally reaches the lungs and is exhaled via the lung alveolas.

The xenon technique has been used for liver blood flow studies in man (Gelin et al., 1968; Sherriff et al., 1977) and experimental animals (Rees et al., 1964; Darle, 1970; Smith and Clarke, 1976; Thorne et al., 1979). The isotope has been administered by injection either directly into the liver parenchyma, or into the portal vein system or the hepatic artery. The conclusions regarding which part of the liver flow that is measured with the various injection techniques differ from study to study, as well as the mathematical methods to analyze the washout-curves.

Mathematics

At the mathematical analysis of xenon washout-curves, the organ of study is usually modelled as a system of parallel compartments, where each pool represents a specific type of tissue with respect to blood perfusion or partition coefficient. If no recirculation of the xenon occurs, the washout from each pool is exponential:

$$C(t) = C(t_0) \exp\left(-\frac{f \cdot t}{\lambda}\right) \quad (1)$$

where $C(t)$ is the observed count rate at time t , f is the specific tissue blood flow in the dimensional units ml/min

per gram of tissue and λ is the partition coefficient. For liver studies, several investigators have reported on two components in the clearance curve (Darle, 1970; Sherriff et al., 1977). For a parallelly two-compartment system, the washout of xenon following a bolus injection is:

$$A(t) = P_1 \cdot \exp(-k_1 \cdot t) + P_2 \cdot \exp(-k_2 \cdot t) \quad (2)$$

where $A(t)$ is the xenon activity in the organ at time t . P_1 and P_2 , respectively, are the initial amounts of xenon in each compartment and k_1 and k_2 , respectively, are the elimination rates of the two components. By multiplying each k_i with the partition coefficient of the tissue in question, λ_i , the specific blood flow of each compartment is obtained.

Aim of the study

The purpose of this investigation was to study the reliability and suitability of the xenon-washout technique on rat liver. Different injection techniques were used to administer the activity to the liver tissue. The study was initiated with the ultimate goal to find a suitable technique for assessment of liver blood flow at experiments with hyperthermia as a new treatment concept for liver cancer. During hyperthermia, the blood flow has the important role of distributing and transporting the heat. For that reason, a simple and reliable method for repeated studies of relative changes in blood flow is required.

2. Materials and Methods

Twenty-five Wistar rats weighing 150-215 g were used for the experiments. The animals were kept under general anesthesia (Nembutal) with one liver lobe exteriorized through a midline incision. 1-10 MBq of Xe-133 in 0.1 ml saline was used as the tracer. A total number of 77 blood flow measurements were performed on the 25 experimental animals. Three techniques for administering the activity to the liver tissue were used:

Series 1: Injection via the portal vein (8 animals, total of 31 runs). A catheter (outer diam.: 0.63 mm) was introduced through a distal branch of the superior mesenteric vein.

Series 2: Injection via the hepatic artery (7 animals, total of 22 runs). A polyethylene catheter with an outer diameter of 0.61 mm was inserted into the gastroduodenal artery and placed with the tip just caudal to the origin of the hepatic artery.

Series 3: Intraparenchymal injection directly into the liver tissue (10 animals, total of 24 runs).

In series 1 and 2, the catheters were flushed with 0.2 - 0.3 ml saline. The injection of the xenon took place during a maximum of 10 seconds. In series 1 (intraportal injection), measurements on 3 rats (8 runs) were performed with closed abdomen.

The liver blood flow was measured on an average three times on each animal with 30 - 60 minutes between each measurement. The clearance of Xe-133 was measured with a CdTe (Cadmium-Telluride) miniature detector with energy-resolving capability. It was provided with a cylindric lead collima-

tor, 1 cm in diameter and 1 cm in length. It was mounted close to the exteriorized liver lobe - or, for the three rats with closed abdomen, from above to cover the entire liver. Care was taken to minimize overlapping of other regions, especially the lungs. The detector was connected to a data acquisition system which accumulated and stored the incoming pulses in 2 second-intervals. Pulse-height discrimination was used and the energy window was 30 keV symmetrically around the 81 keV gamma peak of Xe-133. The washout-curves were registered for a period of 20 - 25 minutes, counted from the moment of injection. All data was stored on paper tape for later analysis on a minicomputer.

The count rate was normally in the order of 1000 - 5000 s^{-1} at, or shortly after, the injection of the activity. The background was around 1 cps and hence negligible. At repeated studies of the blood flow, small amounts of xenon could still remain in the liver tissue due to previous studies. It was assumed that this xenon reflected the clearance from the slower compartment and could satisfactorily be separated from the fast clearance in the subsequent mathematical analysis of the washout-curve.

The washout-curves obtained were analyzed by using a biexponential approach according to equation 2. This equation was fitted to the experimental washout-curves by using the method of least square. The algorithm used to perform this task was based on the Taylor-series linearisation technique and coded in FORTRAN (Draper and Smith, 1966). Repeated analyses of each washout-curve were performed with successively increased start time of the fit. The start times ranged from time zero (the moment of injection) to 3 minutes later with 10 seconds increased start-time between each new calculation. The mean value of the fast component k_1 from the computations with start times between 1 and 2 minutes after the injection, was taken as the index of the

liver blood flow. This procedure was adopted in order to avoid artefacts in the blood-flow calculations from flushing of xenon through the vascular bed, or from instabilities in the partition coefficient during the first minute of liver-washout as has recently been reported by Kuikka et al., (1980). The spread in k_1 from the repeated analyses was taken as a figure of the precision of the blood flow determination. If the clearance of xenon was exactly biexponential, the repeated analysis should give the same results, whereas an erroneous model would be detected by diverging results. The end-points of the curve analysis were chosen at 11, 16 and 21 minutes after the injection of the activity. Differences in the results by using different end-points in the curve-fitting were also used to indicate eventual failures of the biexponential model.

The fast component, k_1 , can be converted to specific blood flow by multiplying it with the partition coefficient λ , which is approximately 0.7 for liver tissue (Conn, 1961; Andersen and Ladefoged, 1967). With the goal to measure relative changes in the blood flow within the same species and the same organ, this conversion to specific blood flow is, however, not necessary.

The slow component, k_2 , was assumed to reflect low perfused tissue, or tissue with a high partition coefficient (e.g. fat). Its origin was considered to be of less importance for this project and not further analyzed.

3. Results

Typical washout-curves for different techniques for the xenon administration are shown in Figure 1(a-c). The separation into a fast and a slow washout-component according to equation 2 is also demonstrated. The calculated liver blood flows, represented by the fast component k_1 , are shown in Figure 2 (a-c). The histograms show the individual values of k_1 . Intraportal and intraarterial injection of the xenon gave flow indexes with a mean of $0.52 \pm 0.19 \text{ min}^{-1}$ and $0.51 \pm 0.15 \text{ min}^{-1}$, respectively (converted to specific blood-flow, this is $0.36 \text{ ml} \cdot \text{min}^{-1} \text{ g}^{-1}$). Injection of xenon directly into the liver parenchyma gave $k_1 = 0.80 \pm 0.30 \text{ min}^{-1}$ ($0.56 \text{ ml} \cdot \text{min}^{-1} \text{ g}^{-1}$). The difference in k_1 between intraparenchymal injection compared to portal and arterial injection was statistically significant ($P < 0.001$, student T-test). A summary of the experimental data obtained is given in Table 1. The spreads in k_1 between different measurements on the same rat were 27% and 25%, respectively (± 1 SD around the individual mean-value), for portal vein and arterial injection of the isotope and 18% for intraparenchymal injection. There was a slightly higher k_1 in the animals with the liver in ordinary position (0.64 min^{-1}) compared to the animals with exteriorized liver (0.49 min^{-1}).

The magnitude of the second component, k_2 , was $0.06 \pm 0.05 \text{ min}^{-1}$ for all three administration techniques. The relative initial height of the slow compartment, i.e. P_2 relative to P_1 , was 0.15 ± 0.10 for intraparenchymal and intraportal injection, but 0.66 ± 0.25 for arterial injection.

The use of the successively increased start times for the numerical analysis of the washout-curves was found to be a valuable tool to estimate the accuracy in the results. Figure 3 shows two typical outcomes of the fast component k_1

from the analysis. In a significant number of experiments, k_1 dropped rapidly during the first minute after the injection of the isotope and then become rather stable with little or no further decline. Other experiments gave stable k_1 during the entire analysis. The uncertainty in k_1 due to spread between the analyses with different start times between 1 and 2 minutes, was less than 10% for all three injection techniques.

The use of different end-points of the fit generally gave 10% higher k_1 when the analysis was performed during 1-11 minutes of washout, compared to 1-16 minutes analysis. The latter also gave 10% higher k_1 compared to 1-21 minutes analysis. In some of the experiments with portal- or arterial injection of the isotope, a very rapid component was evident, but was believed to be caused by direct flushing of xenon through the vascular bed of the liver.

4. Discussion

The differences in the results between analyses carried out with different end-points of the fit are not in accordance with the pure biexponential model. Too early start of the analysis gave also rise to discrepancies with the biexponential model. It seems therefore, that the two-compartment model is a simplification, but is, nevertheless, convenient for assessment of the blood flow in rat liver since the discrepancies were small and the method is easy to use. The calculated blood flow is, due to this disagreement, more of an index than an absolute flow because its value is dependent on how the mathematical analysis is carried out. The conditions for the analysis of the washout-curves must therefore be very clearly defined since the choice of start- and end- time of the fit affects the outcome of the calculation. Otherwise, absolute comparisons to other results obtained with Xe-technique will be misleading. The observed sensitivity of the bi-exponential model to different start- and end-times of the fit has also been reported for regional cerebral blood flow measurements in man (Meric et al., 1977).

Large variations in the fast component, k_1 , (18 - 27%) were found between repeated studies in the same animal. If this is due to physiological variations within the liver or to methodological limitations of the xenon technique, could not be established by the present study. The corresponding spread in Darle's data (1970) on cat liver (portal vein injection) was 18%. Smith and Clarke (1976) studied the Xe-technique on rat liver (hepatic artery injection) and found the spread in k_1 on the same animal to be 19%. Hollenberg and Doughert (1966), used Kr-85 for liver blood flow measurements on dogs. They found a variation of 10% between consecutive studies (both portal vein and arterial injection of the isotope). On man, Sherriff et al. (1977),

found a mean deviation of 7% at repeated studies (portal vein injection). Thus, the spread in k_1 between repeated measurements has been observed by previous investigators. This indicates that only larger changes in the liver blood flow pattern can be detected. For this purpose, the xenon technique is valuable since repeated and regional studies on the same organ can easily be performed. If experimental hyperthermia will cause detectable changes in the liver blood flow measured with Xe-technique will be further investigated.

The large relative height of the slower washout-component seen with arterial injection of the xenon may suggest that this route supplies a large volume of either heterogenously perfused liver-tissue or tissue with a large partition coefficient.

The same magnitude of specific blood flows was observed with both portal vein- and arterial injection. This could be taken as evidence that xenon is directly delivered into and washed out from the same sinusoidal bed, independent of the injection route. However, substantially higher specific blood flows were found when the xenon was injected directly into the parenchyma. This implies that the pathways for the distribution of the xenon are more complicated, a conclusion which also was drawn by Hollenberg and Dougherty (1966), and Darle (1970).

The liver is organized with the arterial and portal venous blood travelling separately within the interlobular connective tissue before they are mixed in the sinusoids. In the rat, anastomosis and capillary networks between the two systems have been observed in the interlobular course (Hase and Brim, 1966). This supports the suspicion that xenon washout from rat liver tissue, following a portal vein or an arterial injection of the isotope, can be described by

assuming a serially connected system, composed of entrance portal or arterial pools which are tied together in a third pool, the sinusoids (Figure 4). With this model, portions of the xenon injected intraportally or intraarterially are distributed first in the entrance pools and are thereafter re-distributed to the sinusoid-pool. The calculated fast component k_1 , is then a combination of the blood perfusion in both the entrance- and the exit-pools.

The fast specific blood flow observed by using direct injection into the parenchyma can be understood as a parallel and simultaneous administration of activity into all three compartments. A significant part of the injected xenon is administered directly into the sinusoid-pool, and is then immediately available for washout. A high perfusion rate in the sinusoids then results in a rapid washout of xenon.

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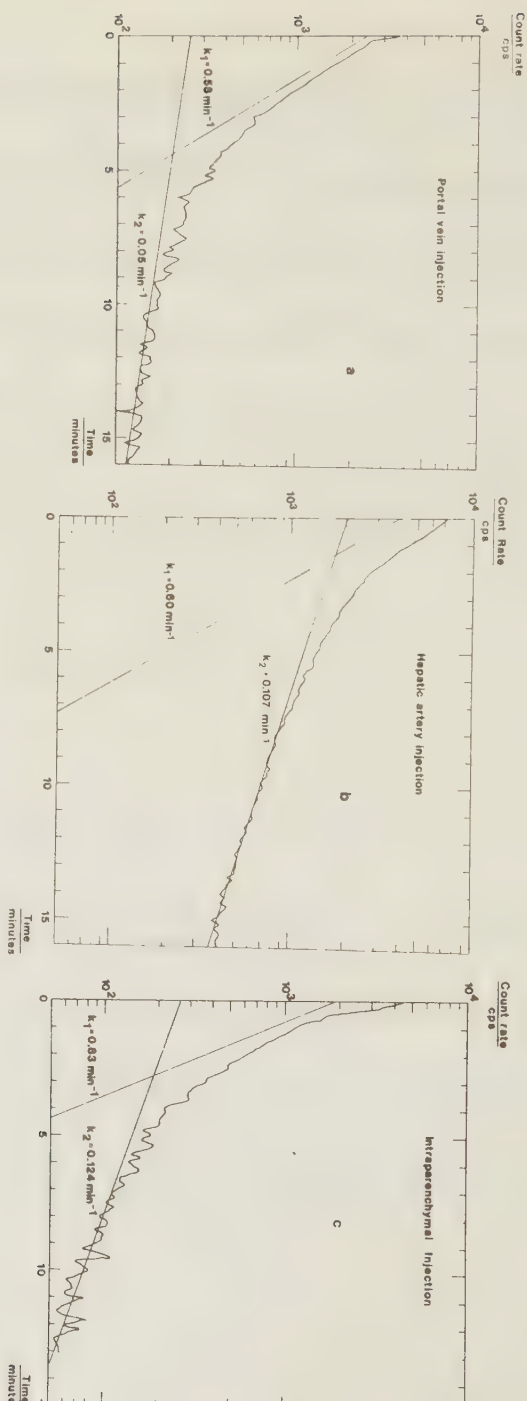


Figure 1. Typical xenon washout-curves following a bolus injection into the portal vein (a), the hepatic artery (b), and directly into the liver parenchyma (c).

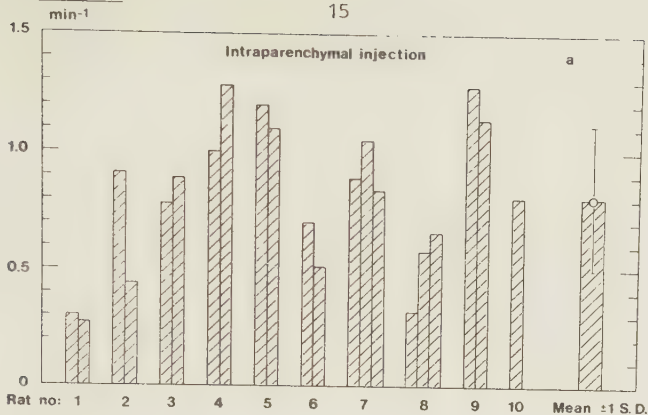
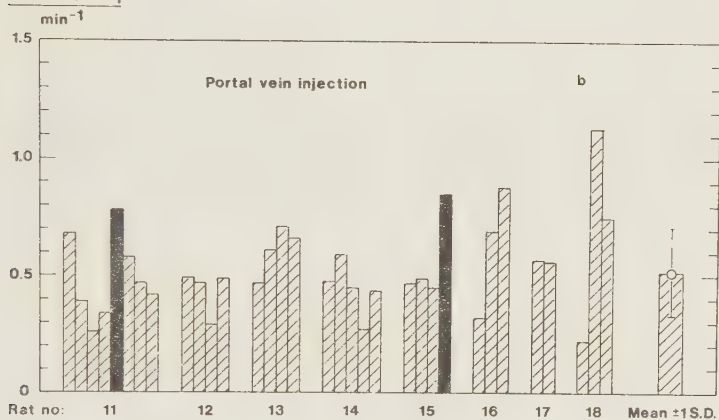
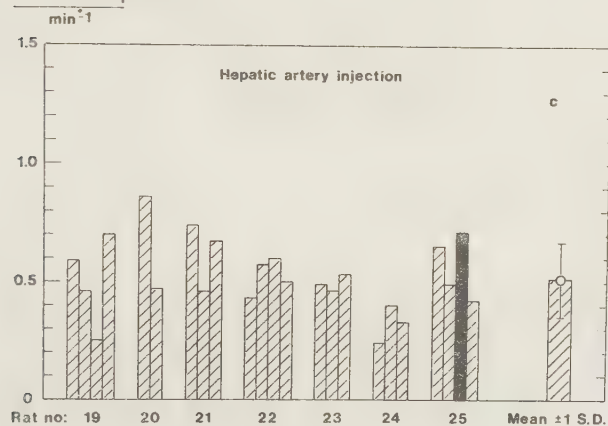
Fast slope k_1 Fast slope k_1 

Figure 2 (a,b,c). Calculated individual liver blood flows, represented by k_1 , for the three administration techniques. The histograms show each individual measurement for all rats. The black-filled staples in Figures b and c represent measurements performed by direct injection into the liver parenchyma.

The liver was in normal position for the rats 16, 17 and 18.

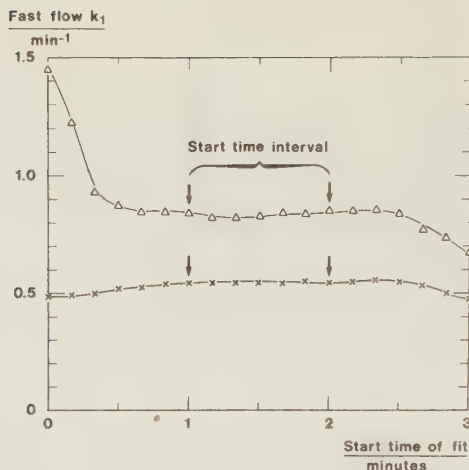


Figure 3. Two typical outcomes of k_1 by using different start-times at the mathematical analysis. The rapid decline of k_1 (the upper curve) during the first minute of washout was usually observed. In other cases (the lower curve), k_1 was constant and independent of the start-time of the analysis. The mean value of k_1 obtained during the first and the second minutes after the injection was used as the index of the blood flow.

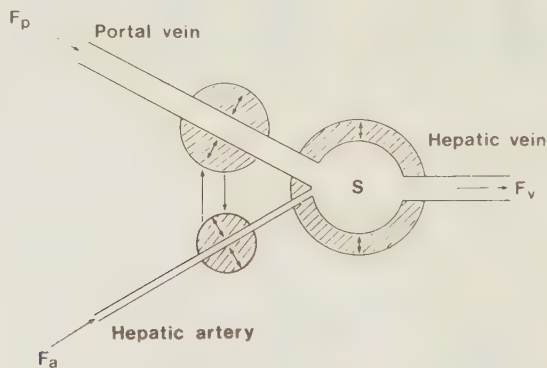


Figure 4. Proposed model of xenon uptake and clearance from liver tissue. The circles which surround both the portal vein and the hepatic artery represent capillary networks in the interlobular course in which blood-tissue gas exchange may occur (indicated by the arrows). Blood-tissue gas exchange also occurs in the sinusoids (S). F_p , F_a and F_v , respectively, are the absolute blood flows (in ml/min) at the portal, arterial and the venous sides.

	Administration technique		
	Portal vein	Hepatic artery	Parenchymal injection
No. of animals	8	7	10
No. of experiments	31	22	24
Mean flow index, k_1 ,	0.52 ± 0.19	0.51 ± 0.15	0.80 ± 0.30
Intra-individual spread (1 S.D.)	27%	25%	18%
Average uncertainty in k_1	7.4%	9.5%	5.6%

Table 1. Summary of the results from the calculations of the liver blood flow in rat.

